



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 58

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

Volume 58 consists of six chapters. John L. Esker and Martin Newcomb of Wayne State University describe radical cyclization routes to pyrrolidines, illustrating some of the significant recent advances which have arisen from the application of radical chemistry to heterocycles.

Two chapters deal with the increasing influence in heterocyclic chemistry of unusual heteroatoms. Igor D. Sadekov and Vladimir I. Minkin of Rostov University (Russia) survey the chemistry of tellurium-containing heterocycles with two heteroatoms, while Allan Blackman of the University of Otago (New Zealand) summarizes the influence of metals on the reactivity of heterocyclic ligands in his chapter, "Reactions of Coordinated Ligands."

The chemistry of highly electron deficient nitrogen heterocycles containing carbonyl groups is covered by Ana M. Costero of the University of Valencia, Spain, in the first overview of this interesting chemistry.

The final two chapters both deal with aspects of the electrophilic substitution of heterocycles. Derek T. Hurst of Kingston University (England) summarizes nitrations which occur in phenyl rings as substituents in heterocycles. Finally, we present the second of the three-part series by M. Ross Grimmett (also from the University of Otago) on the halogenation of heterocycles. This part deals with six-membered heterocycles.

We remind readers that the last "index volume" was Volume 54 of our series and that we expect the next set of indexes to be in Volume 60.

ALAN R. KATRITZKY

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The Generation of Nitrogen Radicals and Their Cyclizations for the Construction of the Pyrrolidine Nucleus

JOHN L. ESKER AND MARTIN NEWCOMB

*Department of Chemistry, Wayne State University, Detroit,
Michigan 48202*

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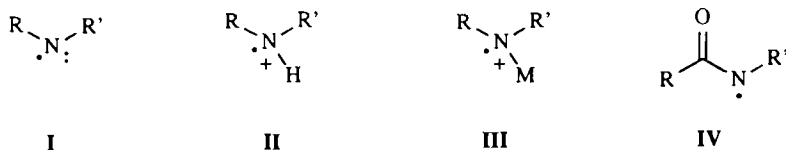
I. Introduction

The use of radical reactions in organic transformations is becoming increasingly popular among synthetic chemists (86M11; 88S417, 88S489). Favorable features most often noted for carbon centered radicals are mild reaction conditions, good regioselectivity in bond forming reactions (5-*exo* cyclizations are favored over 6-*endo*), and the lack of reactivity with many polar functional groups. Recently, highly stereoselective and enantioselective carbon radical transformations have been reported (91ACR296). The methodology of carbon radical generation and subsequent reactions has been thoroughly investigated via tin hydride (68ACR299) dehalogenation and dechalcogenation methods, the addition-fragmentation method of allyl-tin compounds (85TL4079), the thiohydroxamate ester method-Barton method (85T3901), and the atom and group transfer methods (88S417, 88S489).

Nitrogen centered radical reactions are less well developed than those of their carbon relatives even though the potential for nitrogen radical transformations is high in the areas of alkaloid and heterocyclic chemistry of the pyrrolidine nucleus [78T3241; 83AG(E)337]. The purpose of this report is to summarize mechanistic and synthetic studies of nitrogen radicals. Methods for generation of several types of nitrogen radicals and for control of subsequent reactions are presented.

The electronic nature of a nitrogen centered radical, dictated by reaction conditions and/or the radical precursor employed, is crucial to the mode of reaction, to the ability to undergo efficient intramolecular cyclizations or intermolecular additions, and to the products isolated from the radical reaction. The types of radicals discussed in this review include neutral aminyl radicals, protonated aminyl radicals (aminium cation radicals), metal complexed aminyl radicals, and amidyl radicals. Sulfonamidyl and urethanyl radicals are known (71S1; 78T3241), but they are not within the scope of this chapter.

Neutral aminyl radicals (**I**), also referred to as amino radicals, can be considered to be nucleophilic species whereas aminium cation radicals (**II**), metal complexed aminyl radicals (**III**), and amidyl radicals (**IV**) are electrophilic in nature. Greater utility has been observed with electrophilic nitrogen radicals than with neutral aminyl radicals (71S1). Aminyl radicals are easily protonated with Brønsted acids to give aminium cation radicals and readily complex with Lewis acids to form radicals **III**; therefore, control of the reaction conditions is critical to ensure that reactions of interest are occurring from only one species.



R, R' = alkyl, alkenyl, aryl

II. Neutral Aminyl Radicals

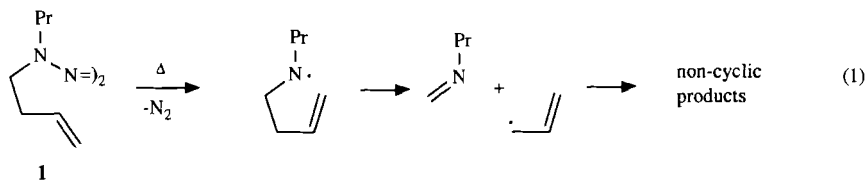
A. DECOMPOSITION OF TETRAZENE PRECURSORS

A direct mode of aminyl radical generation is photolysis or thermolysis of a tetrazene (74JA929; 76JA6728; 79JA7687). However, radicals produced in this fashion do not undergo efficient radical chain reactions because high concentrations of radicals are obtained and usually good chain propagation steps are not available. The reaction pathways available for aminyl radicals thus produced are mainly radical chain termination steps, radical-radical couplings and disproportionations to amines and imines [66JCS(C)813], or reactions with solvent. Neutral aminyl radicals derived from tetrazenes are limited for preparative use by this nonselective behavior, but they have shown their utility in some mechanistic studies. Michejda has shown that these radicals exhibit nucleophilic character as indicated by a positive Hammett correlation ($\rho = +0.69 \pm 0.03$) in the addition reactions of dimethylaminyl radical derived from tetramethyl tetrazene (TMT) with substituted α -methyl styrenes (77TL577).

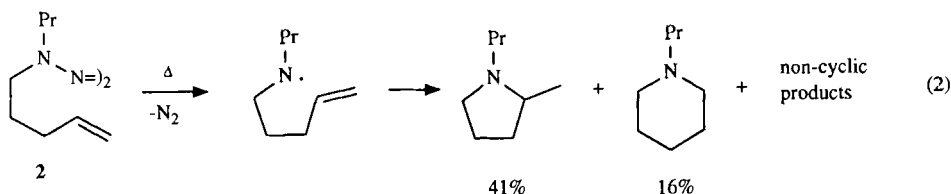
B. AMINYL RADICAL CYCLIZATIONS

Intramolecular cyclizations of alkenylaminyl radicals produced from tetrazenes have been reported. The regioselectivity of cyclizations of aminyl radicals derived from *N*-3-butenyltetrazene (1), *N*-4-pentenyl tetrazene (2), and *N*-5-hexenyl tetrazene (3) have been studied (78MI1). The position of the alkene moiety is important because other reaction pathways can compete with cyclization.

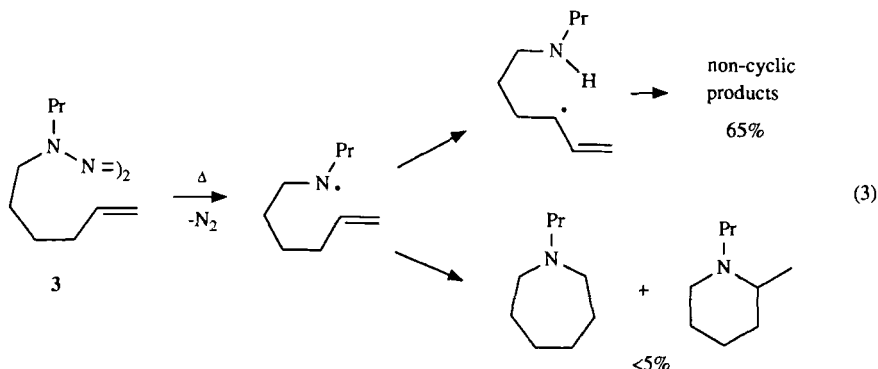
Reactions of the 3-butenyltetrazene led primarily to β -scission products rather than products of 4-*exo* or 5-*endo* cyclizations; thus, the imine and cross-combination products of the allyl radical were obtained [Eq. (1)].



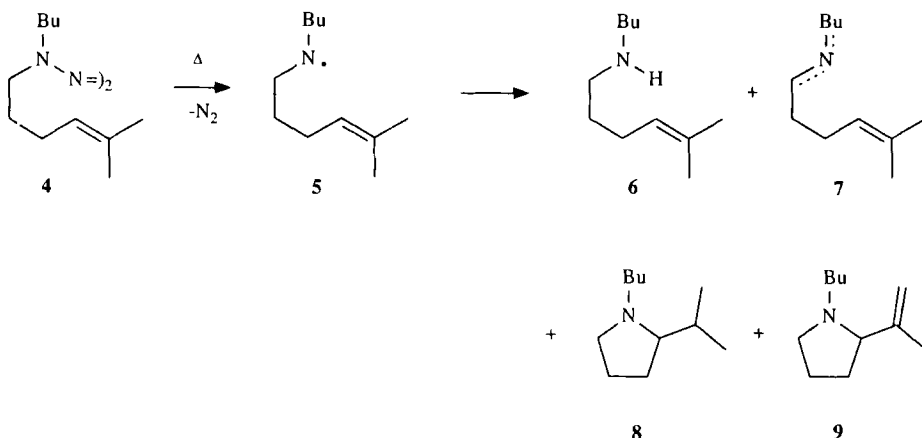
Thermolysis of tetrazone **2** in cyclohexane has been reported to give the cyclic pyrrolidine and, presumably, the piperidine in 41 and 16% yields, respectively [Eq. (2)]. The formation of these reduced products must result



from hydrogen donation by another species, either from disproportionation of the cyclic radicals with other carbon or nitrogen centered radicals or from H-atom abstraction from the solvent. The *N*-5-hexenyl radical, generated by the thermolysis of tetrazone **3**, yielded less than 5% of 6-*exo* and 7-*endo* cyclic products due to a 1,5-allylic hydrogen atom abstraction that competed efficiently with the cyclizations [Eq. (3)].



The cyclization of aminyl radical **5**, produced by decomposition of tetrazone **4** (Scheme 1), was investigated, and products were analyzed by GC/MS comparisons to authentic materials. The results are summarized in Table I (83JA7759). It is important to note that no piperidine products were detected and that a 1 : 1 ratio of cyclic-to-acyclic disproportionation



SCHEME 1

products was formed in the thermolysis reactions. The cyclization was highly regioselective for the kinetic 5-*exo* product and was comparable to that of the analogous carbon centered 5-hexenyl radical that gives a 98:2 ratio of 5-*exo* to 6-*endo* products. Kinetic 5-*exo* products are generally favored in radical cyclizations of 5,6-unsaturated systems (80M11).

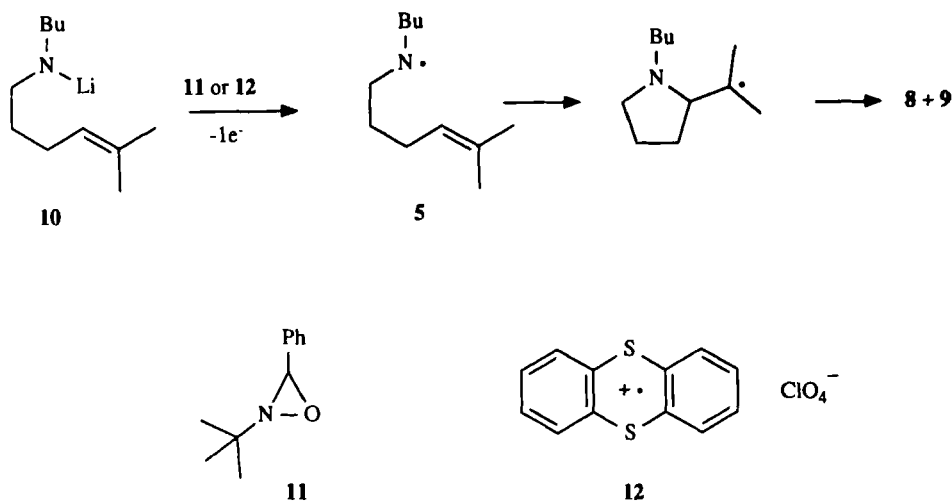
C. OXIDATION OF LITHIUM AMIDES

1. Mechanistic Studies

Aminyl radicals can also be generated from amide bases and organic oxidants via an electron transfer process. The utility of *N*-lithio-*N*-butyl-5-methyl-1-hex-4-enamine (**10**) as a mechanistic probe for such a process was studied (Scheme 2) (88JA6528). The formation of cyclic pyrrolidine

TABLE I
PRODUCT YIELDS FROM THERMOLYSIS OF
TETRAZENE **4**

Solvent	Time (hr)	% Yield			
		6	7	8	9
THF	8	30	9	36	3
Cyclohexane	8	30	9	33	4

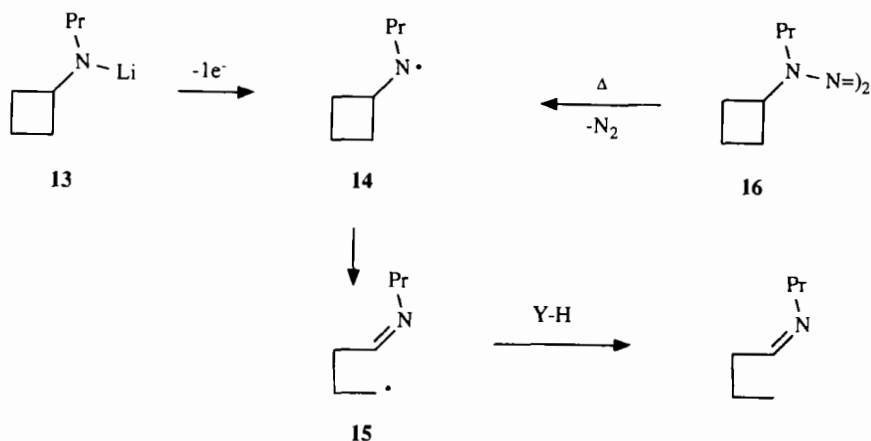


SCHEME 2

products **8** and **9** upon treatment of the amide base with oxidants **11** or **12** suggests that radical **5** was an intermediate because it was established that ionic rearrangement of **10** did not occur under the reaction conditions. The amount of **8** and **9** formed from oxidation of **10** was 13% based on oxidant, and the products were shown to be the same as those formed in the decomposition of tetrazene **4**. The tetrazene decompositions were conducted under relatively nonreactive conditions as is evident from the formation of disproportionated products. However, one cannot be certain that the distribution of products should be the same from oxidation of **10** and decomposition of tetrazene **4**. The formation of cyclic pyrrolidine products from the amide base oxidation is a successful qualitative, although not quantitative, mechanistic probe for aminyl radical intermediates.

N-Propyl-*N*-lithiocyclobutylamine (**13**) also has been used as a mechanistic probe for aminyl radical formation. Upon oxidation, **13** generates the cyclobutylaminyl radical **14**, which undergoes β -scission to give the ring-opened radical **15** (Scheme 3) (84TL2723). Ingold and Maeda reported a rate constant for ring opening of **14** to imine radical **15** of $5 \times 10^5 \text{ s}^{-1}$ at 50°C (80JA328). The imine produced by H-atom abstraction by radical **15** is also the major product of the aminyl radical **14** derived from tetrazene **16** (84TL2723).

The use of lithium amides from *N*-butyl-4-pentenylamine (82TL4867) and *N*-propylcyclopropylamine (82TL4863) as mechanistic probes for radi-

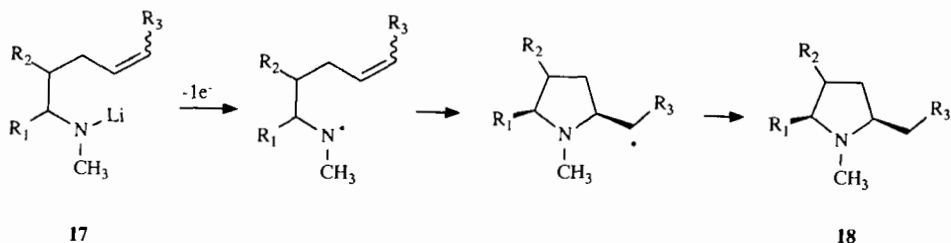


SCHEME 3

cal intermediates in electron transfer reactions was precluded by anionic reactions that led to the same skeletal reorganization as the radical rearrangements.

2. Synthetic Studies

Aminyl radicals also can be generated via electrochemical oxidation of amide bases or O-substituted hydroxylamines. Sugimoto has studied radical cyclizations involving oxidations of lithium alkenylamides as a route to *cis*-1-methyl-2,5-disubstituted pyrrolidines (85TL6085). Electrolysis of lithium alkenylamide **17a**, generated from the amine and butyllithium at -78°C , led to the formation of **18a**, exclusively *cis*, in 52% yield (Scheme 4). The reactions require 0.25 M LiClO_4 in THF:HMPA (30:1) as the supporting electrolyte. A variety of 2-substituted amines were studied,



SCHEME 4

and the results are listed in Table II. Yields generally were better with 2-aryl than with 2-alkyl alkenylamines. A substituent in the 2 position appears to be necessary because when $R = H$ (**17c**) the cyclic product **18c** was produced in only 6% yield and reducing the temperature during the electrolysis from -10 to -50°C did not increase the yield of **18c** (87T281). The process was highly regioselective and stereoselective in forming *cis*-2,5-disubstituted pyrrolidines from 5-*exo* cyclizations of 4-pentenaminyl radicals. Piperidine products, the result of 6-*endo* cyclizations, were not observed. The high stereochemical outcome of these reactions, which does not parallel that of the less selective 5-hexenyl radical (80CC484), might be due to steric constraints of the reaction on the electrode surface (87T281).

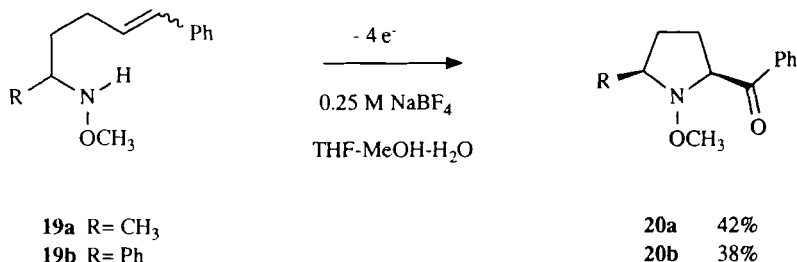
The position of the alkene is crucial for efficient cyclization. Reactions of *N*-lithio-5-hexenamine led to only a trace of the piperidine from 6-*exo* cyclization. Reactions of *N*-lithio-3-butenylamine gave no cyclic products; the acyclic amine and products most likely the result of β -scission were obtained (87T281).

Cyclization of electrochemically generated aminyl radicals is more efficient when the species contains a phenyl-substituted double bond. Evidently, this facilitates cyclization relative to other reactions, and good yields of 5-unsubstituted, 5-alkyl, and 5-aryl-2-benzylpyrrolidines were obtained (Table II, entries 4–6) (91T747). Moderate yields of 4-substituted-2-benzylpyrrolidines also were obtained (entries 7–8). Again, the stereoselectivity was excellent for $R^2 = \text{Ph}$, but it was only 3:1 for $R^2 = \text{CH}_3$.

The apparent dichotomy between good yields of pyrrolidine products from anodic oxidation of lithium alkenylamides and the generally low reactivity of neutral aminyl radicals toward cyclization might be explained by the presence of lithium cations in the electrochemical reactions. The lithium cation has been shown to act as a Lewis acid in promoting aminyl

TABLE II
PRODUCTS FROM ANODIC OXIDATION OF LITHIUM ALKENYLAMIDES

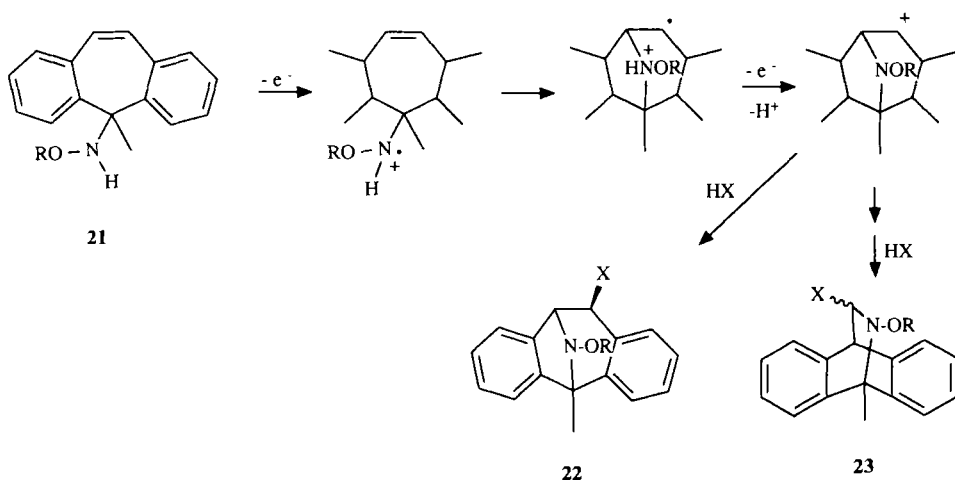
Entry	Li amide	R ¹	R ²	R ³	% Yield of 18	Reference
1	17a	Ph	H	H	52	85TL6085
2	17b	CH ₃	H	H	31	85TL6085
3	17c	H	H	H	6	87T281
4	17d	H	H	Ph	70	91T747
5	17e	CH ₃	H	Ph	85	91T747
6	17f	Ph	H	Ph	66	91T747
7	17g	H	CH ₃	Ph	57	91T747
8	17h	H	Ph	Ph	45	91T747



SCHEME 5

radical reactions (91TL6493). The effect of protic and Lewis acids on the cyclization of aminyl radicals is discussed later in this review.

Direct anodic oxidations of alkenylamines $R_2\text{NH}$ failed to give cyclic products (87T281; 91T747). However, *N*-methoxylalkenylamine **19** cyclized to give *N*-methoxyl-5-substituted-2-benzoylpyrrolidines **20** in useful yields upon oxidation (Scheme 5) (91T747). Under these conditions, the carbon radical resulting from the cyclization reaction was further oxidized, rather than reduced as was the case in oxidations of lithium alkenylamides. Direct anodic oxidation of unsaturated hydroxylamines was used as the key step in the synthesis of the 11-hydroxy metabolite of the important *N*-methyl-D-aspartate receptor antagonist MK-0801 (89TL2191). It was noted that *O*-substituted hydroxylamines (**21**) were required for the reaction in Scheme 6. The reaction is based on a single electron anodic oxida-



SCHEME 6

tion to generate nitrogen centered aminium radical. Even though the reaction conditions are neutral, this radical is most likely the species that cyclizes. The benzylic radical undergoes a second oxidation step to generate a benzylic cation that is trapped by a nucleophile from the less hindered *exo* face to generate **22**. The proposed formation of the carbocation intermediate is supported by the production of rearranged product **23** at low nucleophile concentrations. The yield of **22** was fair to good, depending on the substituted hydroxylamine and nucleophilic trap. The results are summarized in Table III. Optimization using a flow cell design and a conditioned high surface area anode gave **22a** in 75% on a 200 g scale (91T757).

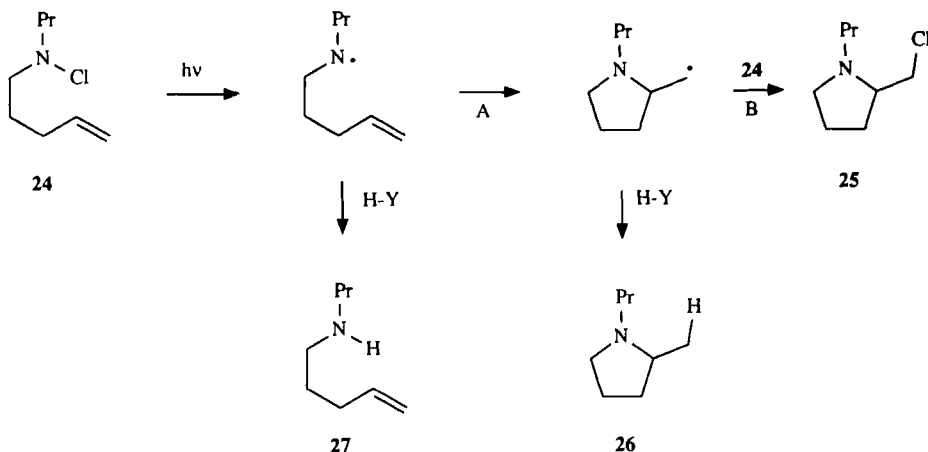
D. AMINYL RADICALS FROM *N*-CHLORAMINES AND *N*-NITROSAMINES

The use of *N*-chloramines, in principle, allows the facile generation of aminyl radicals upon UV photolysis in neutral media. A radical chain can be envisioned for the formation of 2-chloromethylpyrrolidines (Scheme 7). In practice, however, there is a slow step in this sequence, step A and/or B, such that other reaction pathways, disproportionation or H-abstraction from the solvent, compete. Surzur has studied the reaction in Scheme 7 in the alcoholic solvents MeOH and *i*-PrOH, which serve as hydrogen atom sources, and achieved acceptable ratios of cyclic products **25** and **26** to acyclic amine **27** (70TL3107). Other *N*-chloroalkenylamines gave similar results (71TL903; 80TL287). β -chloro-substituted amine products such as **25** were the sole products when the reactions were carried out in acetic acid–water mixtures; these reactions involve aminium cation radicals and are discussed further in Section III,B.

Nitrosamines, unlike nitrite esters, do not undergo cyclizations or other radical reactions upon photolysis in neutral conditions (73ACR354). Pre-

TABLE III
PRODUCTS FROM ANODIC OXIDATION OF
HYDROXYLAMINES **21**

Product	R	X	% Yield
22a	CH ₃	OH	55
22b	Ac	OH	70
22c	CH ₃	OCH ₃	40
22d	CH ₃	OAc	73

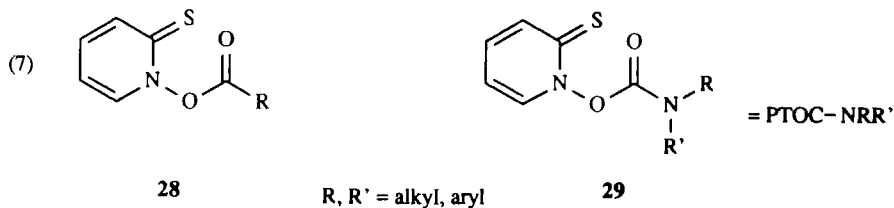


SCHEME 7

sumably, the aminyl radical and the nitrosyl radical, $\text{NO}\cdot$, are generated during photolysis but recombine faster than other reactions of the aminyl radical (64TL1221).

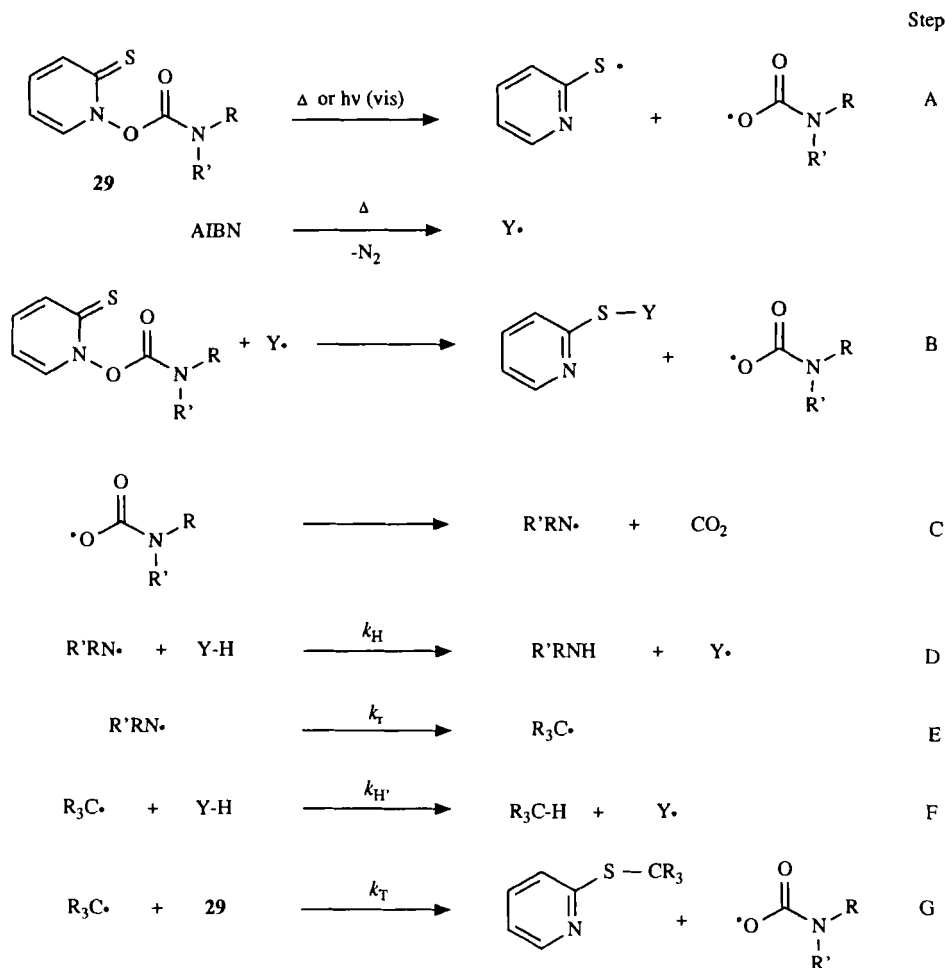
E. AMINYL RADICALS FROM *N*-HYDROXYPYRIDINE-2(1*H*)THIONE CARBAMATES

The acyl derivatives of *N*-hydroxypyridine-2(1*H*)thione, termed PTOC esters (**28**), developed by Barton *et al.* (83CC939; 84CC242, 84CC1298, 84H1) have been widely used for the generation of carbon radicals. This methodology, which permits facile generation of radicals, has been expanded to produce aminyl radicals from the carbamate derivatives of *N*-hydroxypyridine-2(1*H*)thione, termed PTOC carbamates (**29**) (85TL5651). (PTOC is an acronym for the pyridine-2-thioneoxycarbonyl group.)



1. Radical Chain Reactions

The mechanism of aminyl radical generation from PTOC carbamates follows closely the radical chain mechanism of alkyl radical generation from PTOC esters. The chain reaction sequence involves the series of steps shown in Scheme 8. Several methods for inducing N'—O bond cleavage are possible. Photochemical decomposition of **29** via visible light irradiation is used to initiate the chain reaction sequence at ambient or subambient temperature; reactions have been run as low as -78°C (91TL6493).

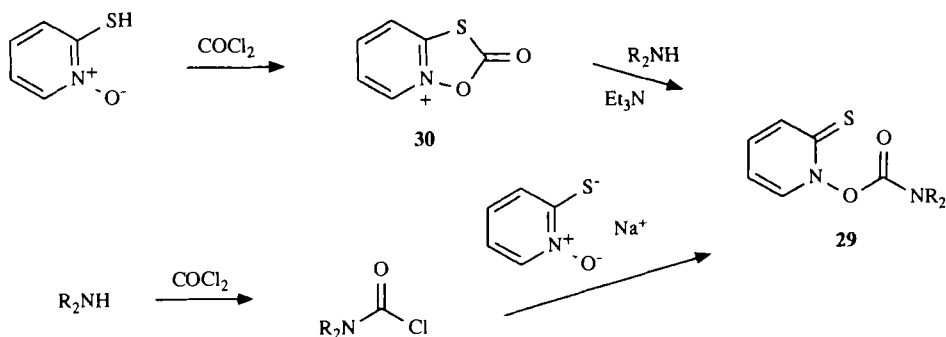


SCHEME 8

Thermal decomposition of **29** in refluxing benzene or toluene or azo-*bis*-isobutyronitrile (AIBN) initiated radical chain reactions employing either Bu_3SnH or *t*-BuSH as chain propagating agents also can be used.

Once initiated, the chain sequence comprises attack of radical $\text{Y}\cdot$ on **29** to give Y-S-pyr and a putative carbamoyloxy radical that rapidly (or synchronously) decarboxylates to generate an aminyl radical. Although, the carbamoyloxy radical is believed to be a discrete intermediate, its lifetime is too short for detection (88JA6727); therefore, loss of CO_2 is essentially concerted (steps B + C). In the presence of a good hydrogen atom source, the aminyl radical can be trapped to give amine and chain carrier $\text{Y}\cdot$. For appropriate substrates, radical rearrangement can occur by cyclization or ring opening to generate a carbon centered radical. Steps E–G now become important. The aminyl radical does not react rapidly with its precursor (85TL5651), so there is no aminyl radical reaction equivalent to steps B or G. Radical chains are terminated by radical–radical coupling and disproportionation at diffusion controlled rates, so the concentration of radicals must be kept low by efficient propagation steps and controlled initiation.

The general procedure for the preparation of PTOC carbamates is outlined in Scheme 9 (85TL5651). Treatment of commercially available 2-mercaptopyridine-*N*-oxide or its Na^+ salt with phosgene generates the adduct pyridinium salt **30**. This salt is stable for periods of up to a year when protected from light and moisture. PTOC carbamates are generated from this salt upon treatment with a nucleophilic secondary amine. For hindered amines, it may be necessary to form a carbamoyl chloride from reaction of the amine with phosgene; subsequent treatment of the carbamoyl chloride with 2-mercaptopyridine-*N*-oxide Na^+ salt gives **29**. These light-sensitive aminyl radical precursors can be isolated in subdued light,



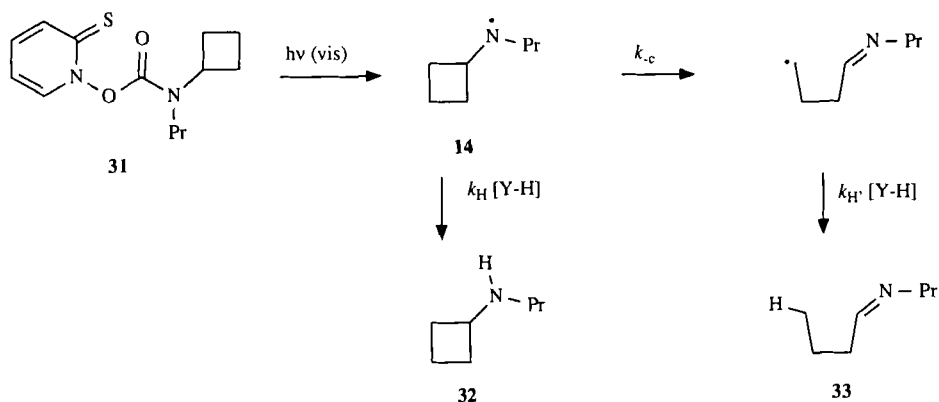
SCHEME 9

and they can be purified by chromatography on silica gel with only partial decomposition. Most are crystalline compounds that can be stored for months.

2. Kinetic Studies

The PTOC carbamate method for efficient and controlled generation of aminyl radicals allows kinetic studies that previously were not possible with tetrazene precursors. As is the case with carbon radicals, optimum synthetic utility of chain reaction sequences is found when absolute rate constants or ratios of rate constants for competing reactions are known, i.e., Scheme 8, step D vs step E. If an absolute rate constant is known for one reaction, then other absolute rate constants can be determined for other reactions from the product distributions in competitions of the reactions of interest with the reaction with a known rate constant.

The second-order rate constants for trapping of an aminyl radical produced from a PTOC carbamate with the hydrogen atom donors *t*-BuSH and Bu₃SnH have been studied by the competition reaction sequence in Scheme 10. In reactions of PTOC carbamates where carbon radicals are ultimately generated, step G in Scheme 8 may complicate the competition, but this step is negligible when a large excess of Bu₃SnH or a faster H-atom donor is used (88JA6528). The rate of ring opening of **14** (k_{-c}) was studied by Ingold and Maeda (80JA328) and determined to be $5 \times 10^5 \text{ s}^{-1}$ at 50°C. The ratio of the unimolecular rate constant for ring opening of **14** (k_{-c}) and pseudo-first-order rate constant for trapping (k_H) was determined from product distributions using the equation $\%33/\%32 =$

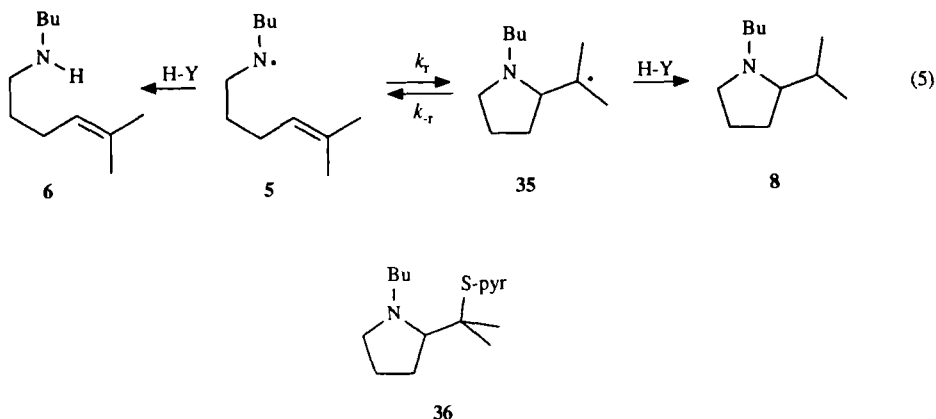


SCHEME 10

(k_{-c}/k_H) \times [trap] $^{-1}$. At 50°C with *t*-BuSH as the trapping agent, the ratio k_{-c}/k_H was $5 \pm 1 M$, which gives $k_H = 2-3 \times 10^5 M^{-1} s^{-1}$. In a similar competition study using the less reactive Bu_3SnH , $k_H = 8 \times 10^4 M^{-1} s^{-1}$. The reactivity order of *t*-BuSH and Bu_3SnH with aminyl radicals is similar to the order of their reactivity with carbon radicals; the rate constants for reaction of Bu_3SnH and *t*-BuSH with primary alkyl radicals are 2×10^6 (89JOC4603) and $8 \times 10^6 M^{-1} s^{-1}$ (85JA4594), respectively. A nucleophilic aminyl radical abstracts a hydrogen atom from thiols faster than from tin hydrides due to relative bond energies and a possible polar effect. Trapping by *t*-BuSH, expected to be relatively insensitive to sterics (81JA7739), allowed the rate constant for ring opening of cyclopropylaminyl radical **34** to be estimated at $k_{-c} = 2 \times 10^7 s^{-1}$ at 50°C (85TL5651). Previously, this ring opening was found to be too fast to measure by ESR methods (80JA328).



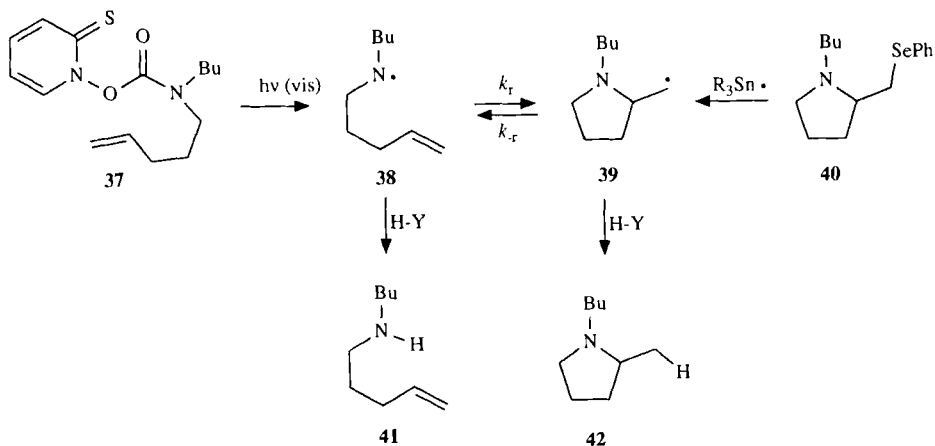
5-*Exo* cyclizations of neutral aminyl radicals were studied in competition with H-atom trapping. Cyclization of **5** was not competitive with H-atom transfer from *t*-BuSH, and only acyclic amine was obtained. However, the rate of cyclization (k_i) of **5** is competitive with the rate of trapping of an aminyl radical with Bu_3SnH . From competition studies involving Bu_3SnH , k_r was determined to be $3.3 \times 10^3 s^{-1}$ at 50°C, but the results suggested that the cyclization reaction might be reversible. A very approximate value for the rate constant of ring opening, k_{-r} , was also calculated



at $7-8 \times 10^3 \text{ s}^{-1}$ at 50°C from a study with a very poor H-atom donor, Et_3SiH , in which an equilibrium was reached between **5** and cyclic radical **35**. With such a poor H-atom donor, step G in Scheme 8 became important, and carbon radical **35** added to the PTOC precursor to generate **36** as a major product along with amine **6**.

Cyclization studies also were carried out with the nor-methyl analogue **37** (Scheme 11). From competition studies employing Bu_3SnH , the rate constant for cyclization, k_r , for **38** was $3.5 (\pm 0.3) \times 10^3 \text{ s}^{-1}$ (90T2317). A more precise value for k_{-r} was determined using β -phenylseleno amine **40**, which was reduced with Bu_3SnH with AIBN initiation. For **39** at 50°C , $k_r = 1.0 (\pm 0.1) \times 10^4 \text{ s}^{-1}$ (90T2317). Not only is the cyclization of neutral aminyl radicals slow relative to cyclization of carbon radicals, but the acyclic radical **38** is favored in the equilibrium ($K_{\text{eq}} = 0.35$). This observation explains erroneous kinetic data for cyclizations of **38** in kinetic ESR studies that estimated the rate of cyclization to be $<5 \text{ s}^{-1}$. In that work, the lower limit for k_r was established by the failure to observe the cyclic radical **39**; however, one now sees that this resulted from an unfavorable equilibrium (80JA328).

The rate constants determined in the kinetic studies described above were derived from relative rate constants. The rate constant for *N*-propylcyclobutylaminyl radical ring opening is the only absolute rate constant known for an aminyl radical. It is possible that this rate constant is only a minimum value and may be in error by up to a factor of 10. The rate constant for H-atom transfer from hydrogen donors to aminyl radicals and those for cyclization and ring opening of aminyl radicals all bear the uncertainty of this initial value. However, the ratios of rate constants



SCHEME 11

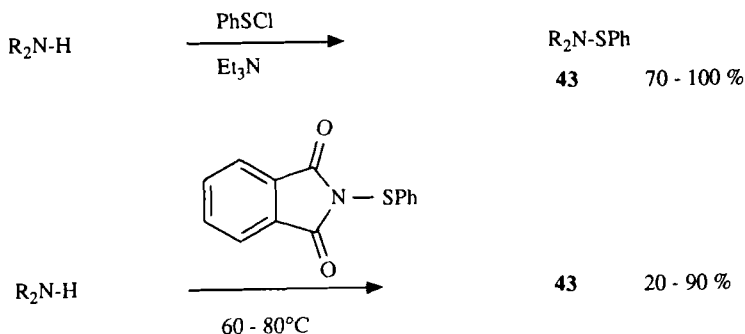
determined in the kinetic studies are not influenced by this uncertainty; for example, the equilibrium constant K_{eq} for **38** and **39** is expected to be reasonably accurate.

F. AMINYL RADICALS FROM SULFENAMIDES

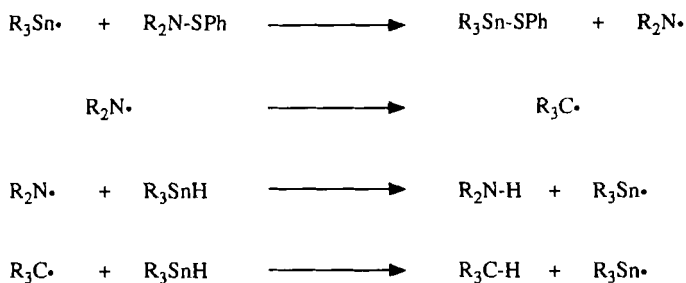
It was recently shown that *N,N*-dialkyl arylsulfenamides **43** generate neutral aminyl radicals in radical chain reactions with Bu_3SnH (91AJC1809, 91TL6441). Sulfenamides have been prepared from numerous routes (79OPP33; 89CRV689). The most facile and high yielding methods appear to be those in Scheme 12. Reaction of amines with benzenesulfonyl chloride (53JA4907) or with *N*-benzenesulfonyl phthalimide (69JOC51) in refluxing solvents gives sulfenamides in nearly quantitative yield. However, some sulfenamides are unstable, and purification methods resulted in significantly lower yields in some cases (91TL6441).

Reactions of sulfenamides with Bu_3SnH initiated by thermolysis of AIBN follow a radical chain sequence similar to $\text{S}_{\text{H}2}$ cleavage of alkyl phenyl sulfides, $\text{R}_3\text{C}-\text{SPh}$, by $\text{Bu}_3\text{Sn}\cdot$ (88S417, 88S489). The sequence of reactions is shown in Scheme 13. The sulfenamide bond, $\text{R}_2\text{N}-\text{SPh}$, is more labile than that of the sulfide analogue under tin hydride radical reduction conditions (91TL6441). Neutral aminyl radicals generated by this method undergo the expected hydrogen atom abstractions from tin hydride, β -cleavage (91TL6441), and sluggish 5-*exo* cyclization (91AJC1809). It was also noted that arylsulfenamides substituted with electron withdrawing groups were more convenient to prepare and handle but demonstrated much lower reactivity toward attack by $\text{Bu}_3\text{Sn}\cdot$ than did simple benzenesulfenamides (91AJC1809).

The use of the thiophilic stannyl radical to cleave an $\text{ArS}-\text{N}$ bond has

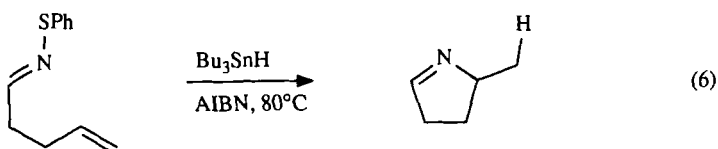


SCHEME 12

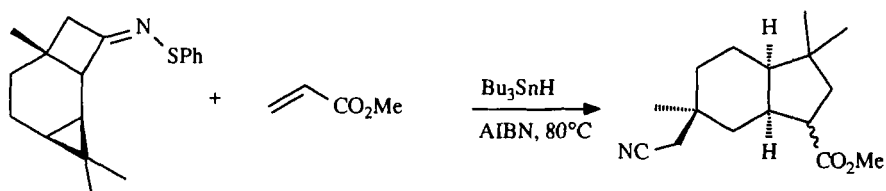


SCHEME 13

also been employed in the preparation of Δ^1 -pyrrolines from cyclization of iminyl radicals derived from arylsulfenyl imines (90TL85). In contrast to the case with neutral aminyl radicals, the 5-*exo* cyclization of a neutral iminyl radical **44** [Eq. (6)] is competitive with reduction by Bu_3SnH . The



carbon radicals generated from iminyl radical cyclization (90TL3545) or from ring opening of cyclobutyliminyl radicals derived from imine **45** [Eq. (7)] (91JA1055) add intramolecularly or intermolecularly to electron deficient alkenes to form mono- and bicyclic Δ^1 -pyrrolines and nitriles.

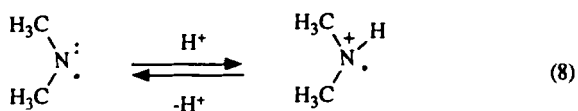


III. Aminium Cation Radicals

A. GENERAL REACTIVITY

Aminyl radicals can be protonated with Brønsted acids or complexed by Lewis acids to generate an electrophilic nitrogen radical. The pK_a of an aminium cation radical in water is ≈ 7 as determined from a titrametric

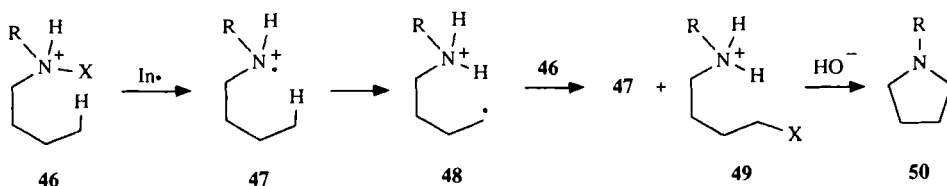
study using ESR methods [Eq. (8)] (72JPC2857). The electrophilic nature of aminium cation radicals (74JA4549) and metal complexed aminyl radicals (77TL577) is supported by negative Hammett correlations, $\rho = -1.29$ and -0.98 , respectively, in addition reactions with substituted styrenes. Aminium cation radicals or metal complexed aminyl radicals show a remarkably different reactivity than do their electron rich aminyl radical progenitors.



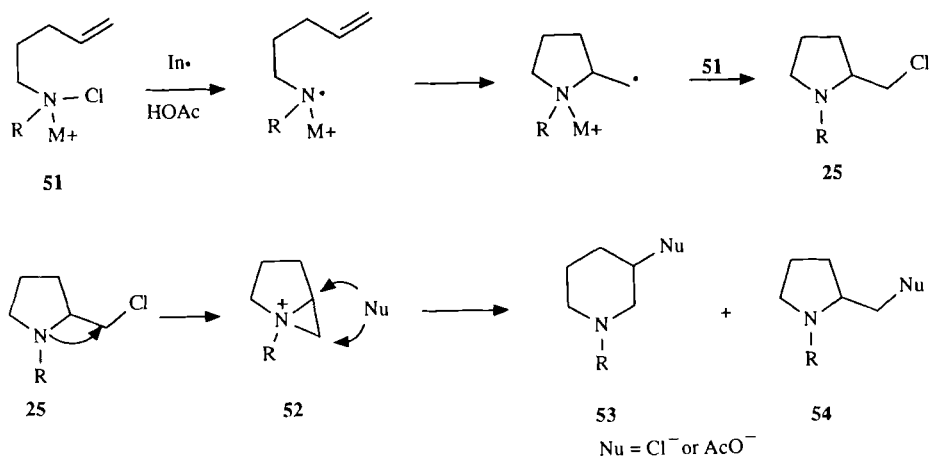
The Hofmann-Löffler-Freytag (HLF) reaction is the oldest known reaction that involves aminium cation radicals (Scheme 14) (50JA2118; 60JA1657). This reaction is a remote functionalization reaction where an *N*-chloro- or *N*-bromo-amine **46** is converted to a δ -haloamine **49** via the intermediate aminium cation radical **47**. Pyrrolidine products are obtained by cyclization of the δ -haloamines under basic conditions. A comprehensive survey of the synthetic utility of this reaction has been reported by Wolff (63CRV55).

B. AMINIUM CATION RADICAL CYCLIZATIONS FROM *N*-CHLORAMINES AND *N*-NITROSAMINES

Electrophilic radical cyclizations of alkenyl aminium cation radicals have shown synthetic utility. Hofmann-Löffler-Freytag reactions do not compete with 5-*exo* cyclizations (75BSF1429). The homolytic cyclization of *N*-chloroalkenylamines under acidic or Lewis acidic conditions has been studied primarily by Surzur and Stella, and the chemistry of these precursors for electrophilic aminyl radical generation has been reviewed [83AG(E)337]. Radical chain reactions can be initiated by heat, UV photol-



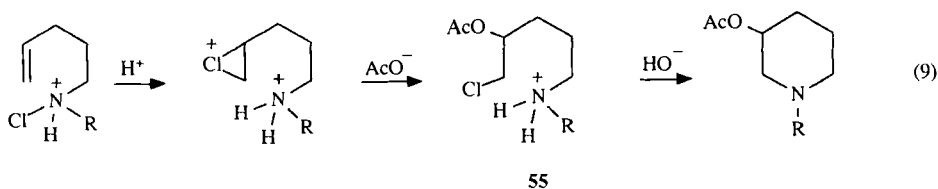
SCHEME 14

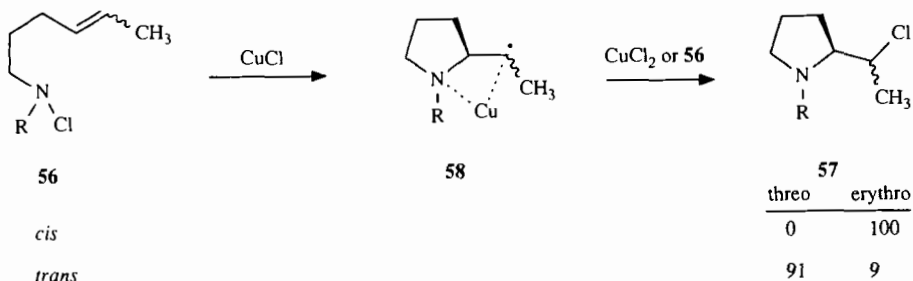


SCHEME 15

ysis, or metal ions. The reactions are carried out under conditions as harsh as $4M$ H_2SO_4 in acetic acid (70BSF115) or as mild as aqueous acetic acid (70TL3107). The chain reaction sequence for *N*-alkyl-*N*-chloro-4-pentenamine (**51**) under these conditions involves an aminium cation radical ($\text{M}^+ = \text{H}^+, \text{Ti}^{3+}, \text{Fe}^{2+}, \text{or Cu}^+$) (Scheme 15) and yields 2-(chloromethyl)-pyrrolidines to the exclusion of other possible radical products (Section II,D). However, these pyrrolidines are nitrogen mustards that are prone to rearrangement to piperidines via aziridinium salts **52**. The yield of piperidines **53** and pyrrolidines **54** is dependent on the nature of nucleophiles present (70BSF115; 71TL903). A variety of stable bicyclic ring systems have been prepared by this method and representative examples are listed in Table IV. *N*-Chloroalkenylamines can also undergo competitive electrophilic chlorination in the absence of efficient radical chain reaction conditions to lead exclusively to piperidine products via **55** [Eq. (9)]. This often complicates products studies from reactions of *N*-chloroalkenylamines in protic acids.

When *N*-chloroalkenylamines are allowed to react with Lewis acidic reducing metal salts (TiCl_3 , FeSO_4 , or CuCl), the radical reaction is more

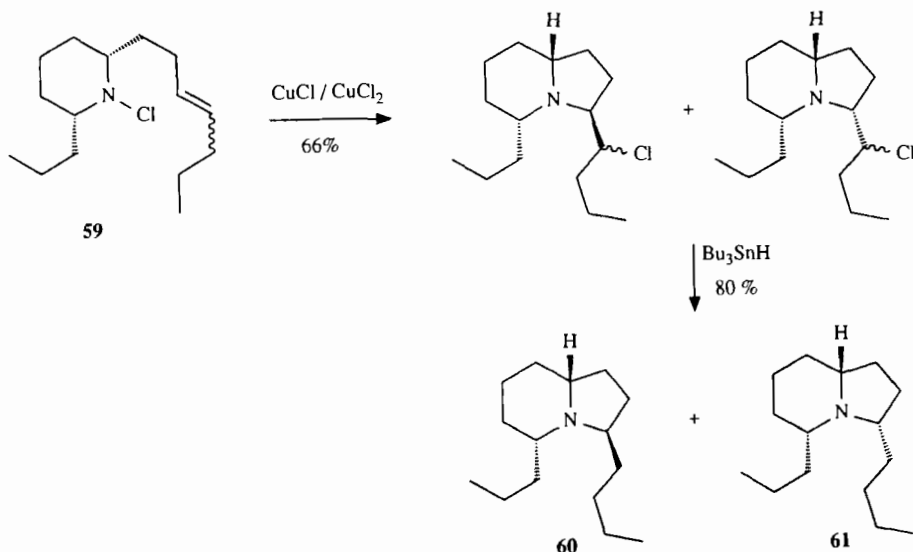




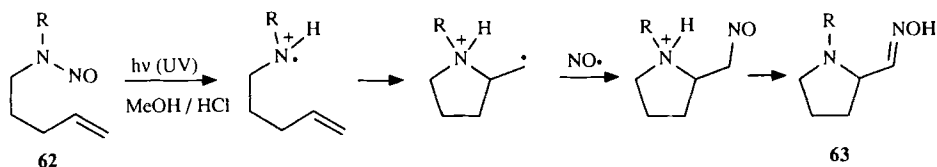
SCHEME 16

efficient, and electrophilic chlorination is not observed. TiCl_3 is generally the reagent of choice, but a redox couple using catalytic CuCl with CuCl_2 provides not only high yields of **57** but also excellent stereoselectivity for the *trans* addition products (Scheme 16). This selectivity appears to be the result of hindered rotation in radical **58** and fast chlorine atom transfer from **56** or from CuCl_2 (81TL61).

The copper complexed aminyl radical cyclization has been used as a key step in a short total synthesis of (\pm)-gephyrotoxin 223AB (**60**). The alkenyl substituted *N*-chloropiperidine **59** was stereoselectively cyclized to construct the indolizidine ring system (Scheme 17) (86JOC5043). Tribu-



SCHEME 17

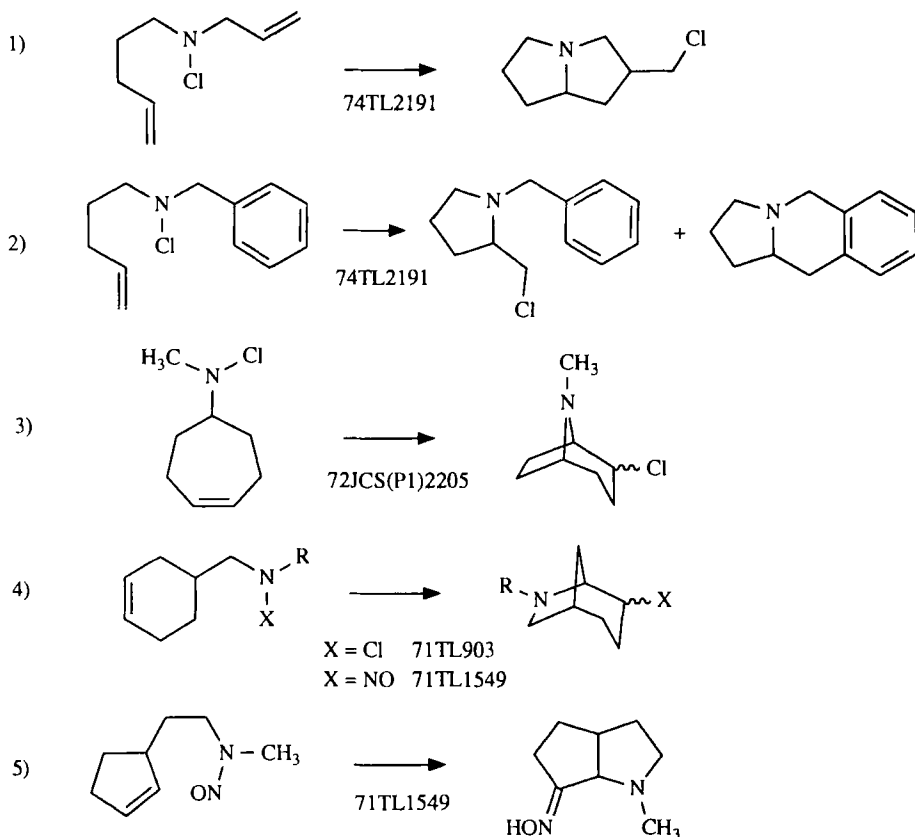


SCHEME 18

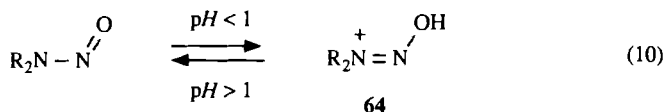
tyltin hydride dehalogenation of the β -chloroamine gave gephyrotoxin (**60**) in a 4.8:1 ratio with **61**.

Aminium cation radical cyclizations can also be accomplished from *N*-nitrosoalkenylamines under mildly acidic conditions (pH > 1). Ultraviolet

TABLE IV
POLYCYCLIC PYRROLIDINE RING SYSTEMS



photolysis of nitrosamine **62** in acidic methanol resulted in a radical reaction that led to nitroso group transfer and, ultimately, oxime products **63** (Scheme 18). Representative examples of this cyclization are included in Table IV. Unlike chloramines, nitrosamines in highly acidic media ($\text{pH} < 1$) do not undergo radical reactions. This is reportedly due to protonation on the nitroso oxygen to form nonphotolabile product **64** [Eq. (10)] (73ACR354) from which the starting nitrosamine is recovered upon neutralization.

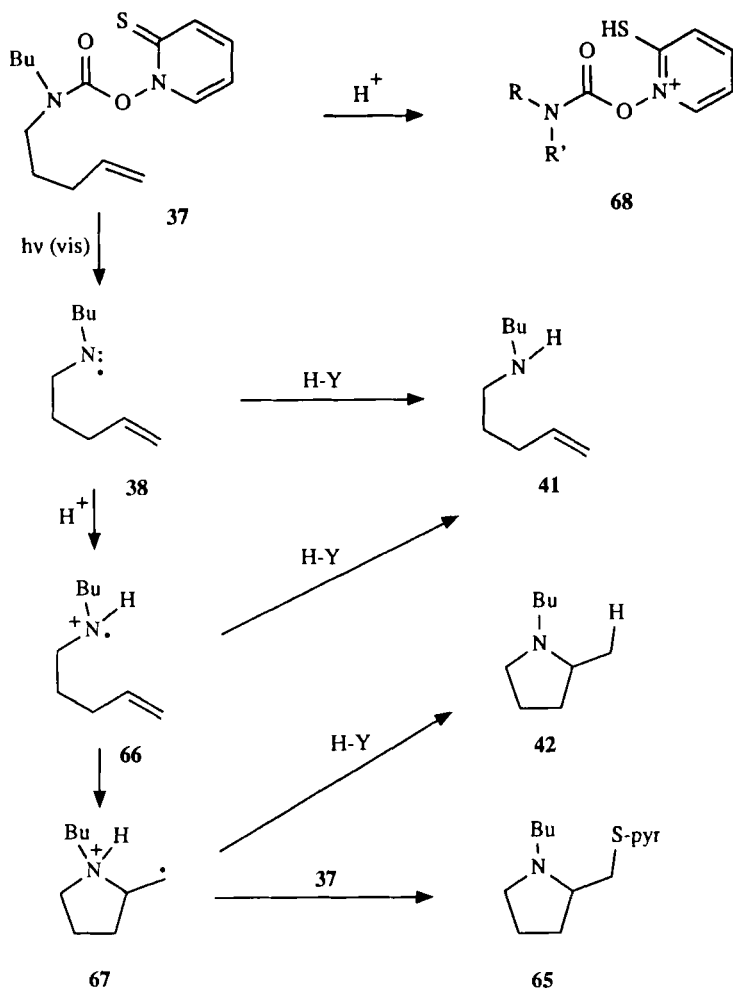


C. DIALKYL AMINIUM CATION RADICALS FROM PTOC CARBAMATES

1. General Reaction Conditions

One of the best methods for the controlled generation of alkenaminyl radicals is via PTOC carbamates (Section II,E). These precursors react in efficient radical chain reactions with hydrogen atom donors to form amines and pyrrolidines. They are stable to anhydrous acids and, therefore, are suitable precursors for aminium radicals produced by protonation of the first-formed neutral aminyl radical.

Studies of the effects of various acids and medium have shown that the identity of the acid and the solvent are important factors in determining the extent of protonation of the aminyl radical and, in turn, the reaction efficiency (87JA3163; 90T2317). The radical chain reaction pathways of PTOC **37** are described in Scheme 19. Trends of aminyl radical reactions are suggested by the results of solvent and acid studies listed in Table V. Aminyl radicals must be partially protonated in benzene with soluble acids because no cyclic product **42** is formed in the absence of acid (87JA3163); however, protonation does not appear to be complete in benzene. With thiol present, **38** partitions between efficient hydrogen trapping by thiol and protonation with cyclization leading to pyrrolidines **42** and **65**. In the absence of thiol, the major reaction pathway is formation of the cyclic "self-trapped" product, pyridyl sulfide **65**. Tetrahydrofuran (THF) was employed as a solvent, but reactions were not appreciably different than those run in benzene. An increase in the dielectric constant for a solvent would be expected to result in more complete protonation for a given acid, and from the results in Table V, acetonitrile is clearly the solvent of choice.



SCHEME 19

The acid is also a critical factor. Acetic acid does not appear to protonate an aminyl radical completely even in acetonitrile. Under highly acidic conditions, the PTOC carbamate may be protonated as was indicated in a study of the simple *N,N*-dipropyl PTOC carbamate. In neat trifluoroacetic acid (TFA), the long wavelength absorbance responsible for the yellow color of the precursor completely disappeared, presumably from protonation at the thione sulfur to form the thiol cation **68** (Scheme 19). The yellow PTOC carbamate was recovered upon neutralization of the TFA

TABLE V
PRODUCT YIELDS FROM PTOC **37** UNDER VARIOUS REACTION CONDITIONS

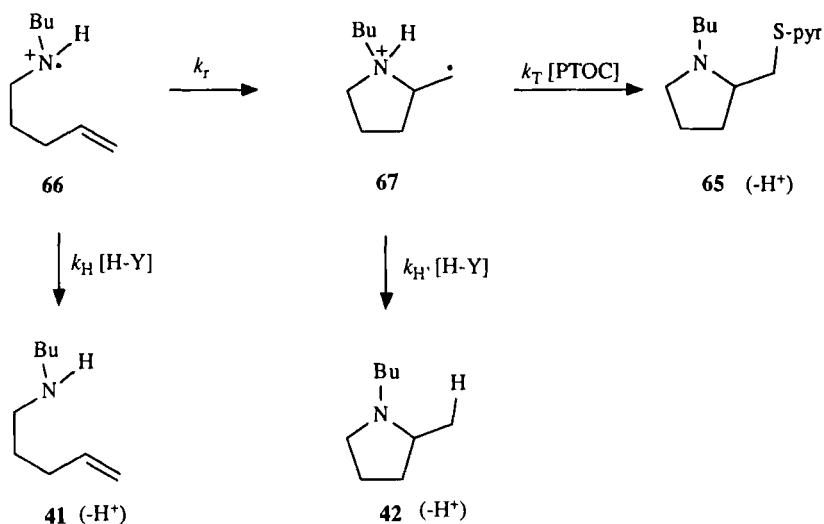
Solvent	0.15 M acid	[<i>t</i> -BuSH] (M)	Relative % yield			Total % yield
			41	42	65	
Benzene	None	0.02	100	0	0	80
	AcOH	0.07	97	2	1	91
	CF ₃ CO ₂ H	0.07	8	23	69	87
	AcOH	None	19	0	81	69
	CF ₃ CO ₂ H	None	6	0	94	85
CH ₃ CN	AcOH	0.07	49	36	15	98
	CF ₃ CO ₂ H	0.07	4	33	62	90
	CH ₃ (CO ₂ H) ₂	0.05	0	43	57	100
	CH ₃ (CO ₂ H) ₂	None	0	0	100	98

reaction mixture (89UPI). Malonic acid is the acid of choice for its ability to protonate aminyl radicals efficiently in acetonitrile without protonating the precursor appreciably and its ease of handling as an anhydrous solid. It is possible that small amounts of acyclic amine **41** arose from acid catalyzed hydrolysis from trace amounts of water in AcOH or TFA.

2. Kinetic Studies of Aminium Radicals

At this time, no absolute rate constants have been determined for a reaction of an aminium cation radical. However, for synthetic utility, one needs to consider the relative rate constants for competing reactions. Competition between two unimolecular reactions depends only upon the relative rate constants for the processes. For competition between a unimolecular and a bimolecular reaction whose rate constants are comparable, product distributions can easily be controlled by the concentration of the second species in the ratio of rate laws. The ratio of reaction products from cyclization (unimolecular) versus hydrogen atom trapping before cyclization (bimolecular) can be expressed by the equation $\%(\mathbf{42} + \mathbf{65})/\% \mathbf{41} = k_r/(k_H[Y - H])$ (Scheme 20). Competition between two bimolecular reactions is dependent on the relative rate constants for each process and the effective, or mean, concentration of each reagent. The ratio of the products from H-atom transfer trapping of the cyclized radical versus self-trapping by the PTOC precursor can be expressed by the equation $\% \mathbf{42}/\% \mathbf{65} = (k_H/k_T)([Y - H]/[PTOC])$.

Contrary to aminyl radicals, aminium cation radicals are not trapped by *t*-BuSH in competition with cyclization. Trapping of the cyclic β -



SCHEME 20

aminium radical **67** with *t*-BuSH (k_{H}) is competitive with self trapping (k_{T}) and $k_{\text{H}}/k_{\text{T}} = 0.3$. Because of this low value, to achieve a ratio of **42**:**65** of 10 or better requires a ratio of thiol to PTOC of 30 or more. With Bu_3SnH , a more reactive hydrogen atom donor toward electrophilic radicals, the aminium radical **66** is trapped in competition with cyclization and $k_{\text{T}}/k_{\text{H}} = 0.33 \text{ M}^{-1}$ (90T2317). Tributyltin hydride also traps **67** more efficiently than does *t*-BuSH relative to self-trapping and $k_{\text{H}}/k_{\text{T}} = 2$. The relative rate constants for reaction of **67** with *t*-BuSH, Bu_3SnH , and PTOC **37** are 0.3 : 2 : 1 (90T2317). The electron deficient character of this radical is apparent when one notes the ratios of rate constants for reactions of a simple primary alkyl radical with the same radical traps are 8 : 2 : 1 (90T2317). This effect is a result not only of a decrease in the reactivity of **67** with *t*-BuSH but also of an enhanced reactivity of the radical with the polar C=S bond in the PTOC as well as with the electron rich H-atom donor Bu_3SnH .

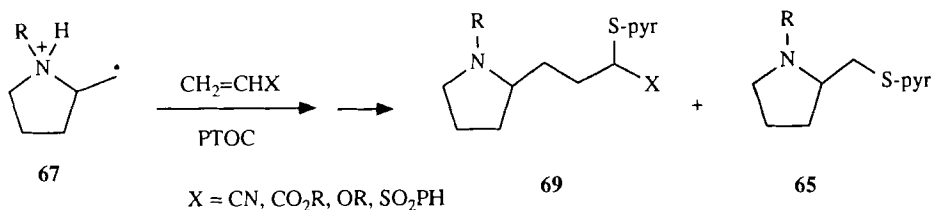
3. Synthesis of Alkaloid Skeletons

A variety of alkaloid skeletons can be prepared from 5-*exo* cyclizations of aminium cation radicals derived from PTOC carbamates, and some are listed in Table VI (90T2329). Perhydroindoles (entry 1), 1-, 2-, and 3-substituted pyrrolizidines (entry 2-4), tropanes (entry 5), and other pyrrolidine containing ring systems were obtained in 50-96% yields. Direct com-

TABLE VI
POLYCYCLIC PYRROLIDINE RING SYSTEMS FROM PTOC PRECURSORS

1)		
	50% 87JA3163	
2)		
	96% 90T2329	
3)		
	90% 90T2329	
4)		
	82% 90T2329	
5)		
	94% 90T2329	
6)		
	86% 90T2329	

parison of this methodology can be made in some cases to reactions of *N*-chloramines [71TL903; 72JCS(P1)2205; 74TL2191] and *N*-nitrosamines (71TL1549). In all cases, the PTOC method was comparable or superior in yield for constructing the ring system.

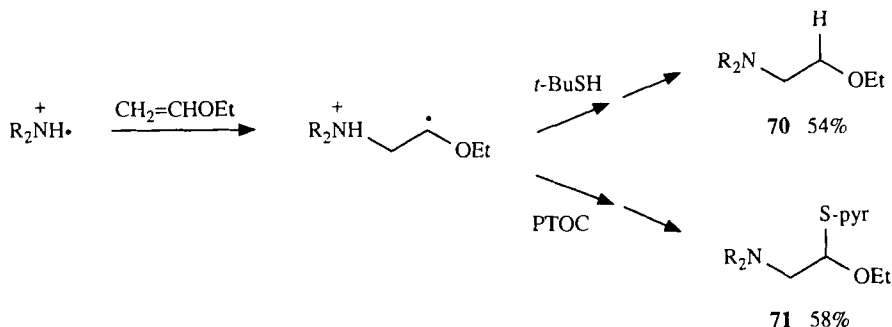


SCHEME 21

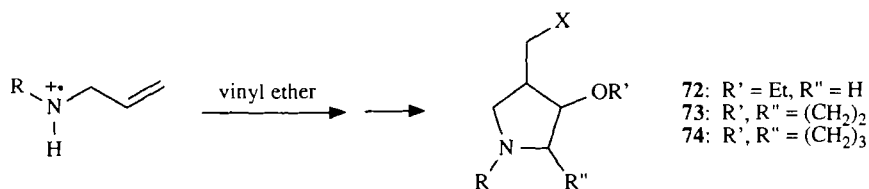
4. Intermolecular Reactions

The trapping of the β -aminium radical **67** with reactive alkenes, acrylates, enones, acrylonitriles, or phenyl vinyl sulfone (Scheme 21) was expected from the analogous addition reactions of carbon radicals generated from PTOC esters (85TL6349; 84TL1055). However, only the very reactive phenyl vinyl sulfone gave good yields of addition product **69** in competition with the self-trapped product **65** (90T2345). This is most likely the result of an increased rate of self trapping of **67** by a PTOC carbamate over that of self-trapping of an alkyl radical by a PTOC ester (90T2317). It is also possible that **67** may suffer a reduced rate of addition to electron deficient alkenes.

Intermolecular addition and addition-cyclization reactions of aminium cation radicals with electron-rich alkenes such as ethyl vinyl ether (EVE) allow an entry into products containing the N—C—O moiety of β -amino ethers **70** or the equivalent of β -amino aldehydes **71**. The mild conditions under which aminium cation radicals are generated from PTOC carbamates makes the reactions described in Scheme 22 possible. In the absence of hydrogen atom donors, the β -amino ethoxy(2-pyridylthio) acetal **71** was the major product. The mixed acetal can easily be converted



SCHEME 22



SCHEME 23

to an acetal by reaction with an alcohol, a procedure that has been used in glycosidation reactions (89TL4283). In the presence of *t*-BuSH, β -amino ethers **70** are formed in good yield.

An *N*-allylaminium cation radical undergoes an addition–cyclization reaction with vinyl ethers in the presence of *t*-BuSH to give 3-alkoxy-4-methylpyrrolidines **72** (Scheme 23) in fair to good yields (90TL1675). In addition to EVE, 2,3-dihydrofuran and 3,4-dihydro-(2*H*)pyran also undergo reactions to give bicycles **73** and **74**, respectively, in reasonable yield.

5. Lewis Acid Complexed Aminyl Radicals from PTOC Carbamates

The PTOC protocol for the preparation of nitrogen centered radicals is also compatible with a variety of Lewis acids that apparently complex with the aminyl radicals to give reactive, electrophilic species. Lewis acids offer potentially milder reaction conditions than protic acids for sensitive compounds. Efficient intermolecular addition reactions have

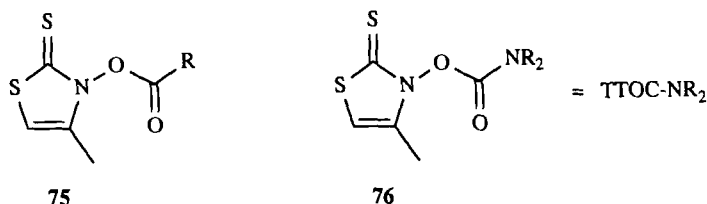
TABLE VII
YIELDS OF PYRROLIDINE **65** FROM LEWIS ACID ACTIVATED REACTIONS OF PTOC **37**

Lewis acid	Equivalent	Solvent	Temperature (°C)	% Yield
LiBF ₄	1.5	THF	22	57
BF ₃ · OEt ₂	1	CH ₂ Cl ₂	22	98
	1		–78	74
	2		–78	98
	0.1		–78	28
	1		–78	97
MgBr ₂ · OEt ₂	0.25		–78	69
Ti(<i>i</i> -PrO) ₃ Cl ₂	0.5		–78	75
Ti(<i>i</i> -PrO)Cl ₃	0.5		–78	98

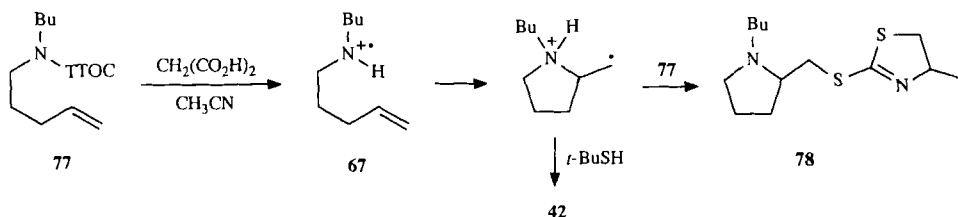
been conducted using fewer equivalents of vinyl ethers when some Lewis acids were employed than when protic acids were used. Lewis acids promote the intramolecular cyclization of aminyl radical **38** in self-trapping reactions to generate **65** (Scheme 19). From the results listed in Table VII, it is clear that in some cases the Lewis acid were true catalysts (91TL6493). However, the binding constants of the Lewis acids with aminyl radicals are not known.

D. DIALKYL AMINIUM RADICALS FROM *N'*-HYDROXYTHIAZOLE-2-THIONE CARBAMATES

Other thiohydroxamic acid derivatives have been used for the generation of radicals. Acyl derivatives of *N*-hydroxythiazole-2-thione (**75**) have been explored by Barton as precursors for carbon radicals [86JCS(P1)39]. It has also been shown that similar precursors can be used for the generation of dialkylaminium cation radicals, *N*-hydroxy-4-methyl-thiazole-2-thione carbamates, TTOC carbamates **76** (91JOC1309). In contrast to



visible light initiation of reactions of PTOC carbamate **37**, TTOC carbamate **77** requires UV irradiation for initiation of the radical chain sequence in Scheme 24. It was also noted from the study of this precursor that the "self-trapping" reaction to generate **78** was not as efficient a chain propagation step as the analogous step in reactions of PTOC carbamates. Yields were better when *t*-BuSH was employed in the reactions; the thiol



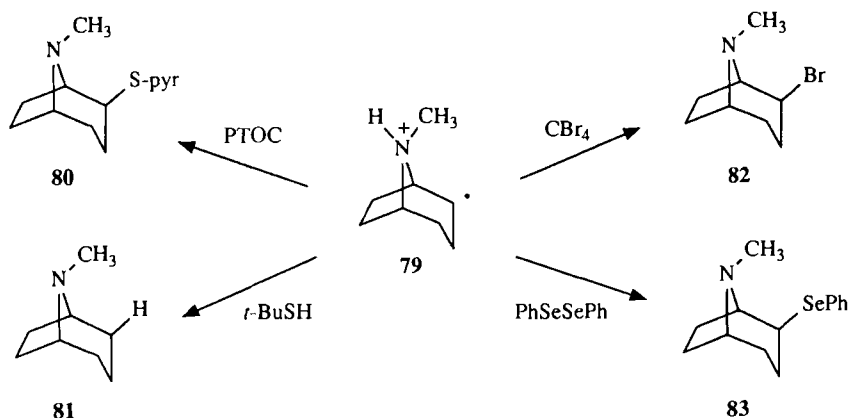
SCHEME 24

apparently led to efficient propagation steps by trapping the carbon radical and providing the *t*-BuS• radical that added to the TTOC precursor.

E. FUNCTIONALIZATIONS OF CARBON RADICALS FORMED BY NITROGEN RADICAL CYCLIZATIONS

Functionalization of the carbon radical resulting from cyclization of an aminium radical is an important step for synthetic chemists in order to obtain the desired product directly or to provide a handle for further transformations. Radical reactions of *N*-chloroalkenylamines (Section III,B) lead to β -chloro pyrrolidines, which are prone to rearrangement to give piperidines. Reactions of *N*-nitroso alkenylamines lead to β -nitroso pyrrolidines and, if an α -hydrogen is present, ultimately to oximes of aldehydes or ketones. Advantages of the latter transformation are the formation of stable substituted pyrrolidines and the utility of the oxime moiety in regard to further transformations.

The use of PTOC carbamates for aminium cation radical generation and cyclization allows the use of other radicophiles to trap the resulting carbon radical. A variety of radical traps for carbon radicals derived from PTOC esters have been assembled (87H449), 87MI1). Many of these trapping agents are also compatible with PTOC carbamates. Representative transformations of **79** are shown in Scheme 25. The self-trapping reaction, forming pyridyl sulfide **80**, is generally one of the highest yielding reactions of PTOC carbamates. Further transformation of this pyridyl sulfide follows the chemistry developed by Barton for functionalization of carbon radicals



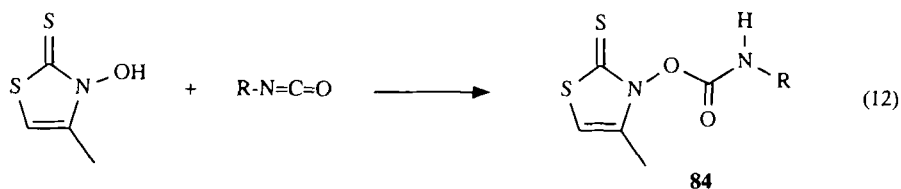
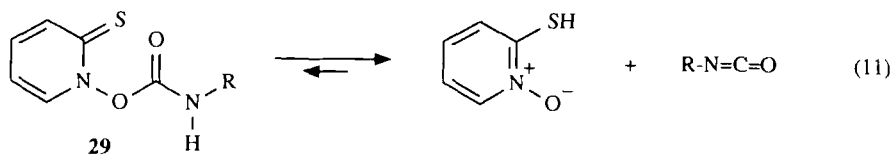
SCHEME 25

derived from PTOC esters. In order to trap cyclic radical **79** with other radicophiles, the rate of trapping must be competitive with that of the self-trapping reaction. Trapping with hydrogen atom donors is competitive (Section III,C,2); the simple reduction of radical **79** to give tropane (**81**) represents a loss of functionality, but the efficient trapping is available (90T2317) and may be desired. Halogenation of **79** with CBr_4 is also possible; this gives 2-bromotropane (**82**). However, halogen atom transfer from CCl_4 or BrCCl_3 is not competitive with self-trapping (90T2345). A simple comparison of the rate constant for reaction of an alkyl radical with Ph_2Se_2 , $k_T = 2.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (83JA1398) with that for reaction with a PTOC ester, $k_T = 1.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ (87TL1615) suggests that phenylseleno trapping should be competitive with self-trapping of the similar PTOC carbamates. The β -phenylseleno amines, such as **83**, are formed in high yields and are not prone to rearrangements that complicate the production of β -halo amines (90T2345). Other group transfer reagents that add to alkyl radicals faster than $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, such as diphenyl ditelluride, $k_T = 1.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ (83JA1398) are expected to trap **79** efficiently, but such a reaction has not been reported. Trapping of **79** with disulfides was not competitive with self-trapping by PTOC carbamates (90T2345). The trapping rate constant for reaction of a primary alkyl radical with Ph_2S_2 , k_T is $1.7 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ (83JA1398). With alkyl disulfides, the rate constants for reactions with alkyl radicals are even slower.

Aminium radical **67**, produced in reactions of TTOC carbamates, can be self trapped in useful yield (Scheme 24). Trapping with hydrogen atom donors and with Ph_2Se_2 are competitive with this self trapping reaction (91JOC1309).

IV. Monoalkyl Aminium Cation Radicals

Monoalkyl aminium radicals cannot be prepared from PTOC carbamates **29** due to an equilibrium in solution favoring 2-mercaptopyridine-*N*-oxide and an alkyl isocyanate [Eq.(11)]. With *N*-(monoalkyl)thiazole-2-thione carbamates, TTOC carbamates, the equilibrium lies far to the side of the carbamate **84**, and these precursors can be prepared from an isocyanate and *N*-hydroxythiazole-2-thione [Eq. (12)]. Under UV photoinitiation in acidic media, TTOC carbamates are efficient precursors for monoalkyl aminium cation radicals (Scheme 26). Monoalkylaminium radical **85** cyclizes as efficiently as its analogous dialkylaminium radical **66**, and the resulting carbon radical **86** can be trapped by a variety of radicophiles (91JOC1309) to prepare substituted pyrrolidines.



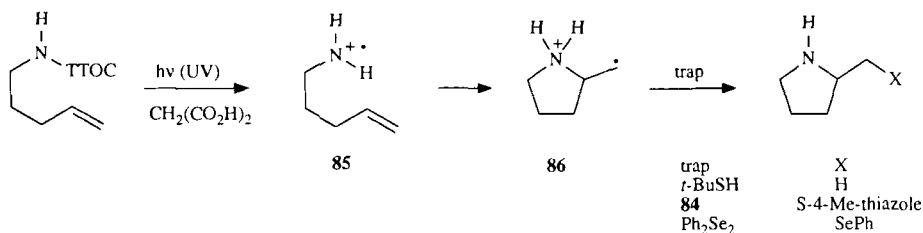
V. Amidyl Radicals

A. REARRANGEMENTS OF *N*-NITROSO- AND *N*-HALOAMIDES

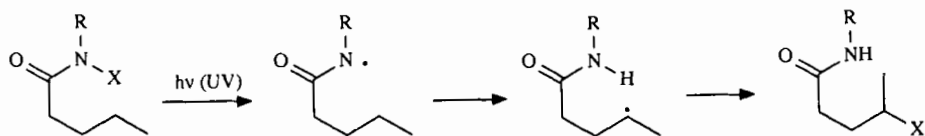
An amidyl radical is intermediate in reactivity between a neutral aminyl and an aminium cation radical due to the electron withdrawing ability of the carbonyl group. An intuitive advantage of amidyl radicals over aminium cation radicals is that reactions can be carried out under strictly neutral conditions, and, by reduction or hydrolysis of the amide, amidyl radical reactions become equivalent to reactions of neutral dialkyl or monoalkyl aminyl radicals. Preparation of *N*-haloamides and their rearrangements have been reviewed (71S1).

1. Remote Functionalization

Saturated *N*-haloamides and *N*-nitrosamides, upon UV photolysis, undergo remote functionalizations δ to nitrogen on the alkyl or, less effec-



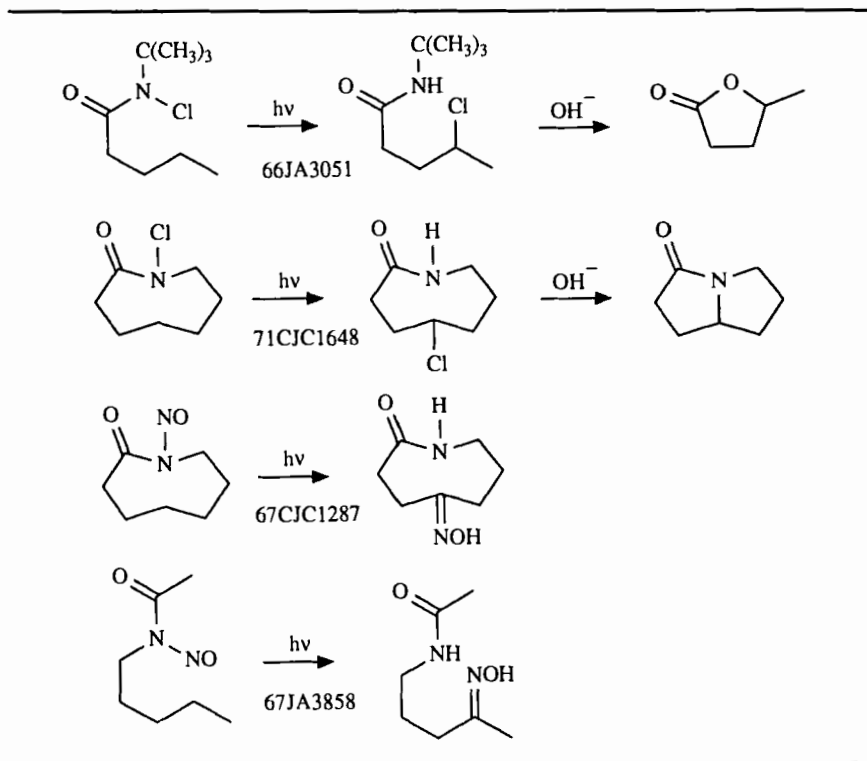
SCHEME 26



SCHEME 27

tively, on acyl side chains (Scheme 27) that are similar to the HLF reaction for aminium cation radicals from *N*-chloramines. *N*-Nitrosamides give δ -oxime products only on the alkyl side chain (67JA3858). Representative examples of the remote functionalization are listed in Table VIII. An interesting transannular reaction of an *N*-nitroso lactam was used for the preparation of a δ -oxime product (entry 3).

TABLE VIII
 δ -FUNCTIONALIZED PRODUCTS FROM *N*-CHLORO- AND *N*-NITROSOAMIDES



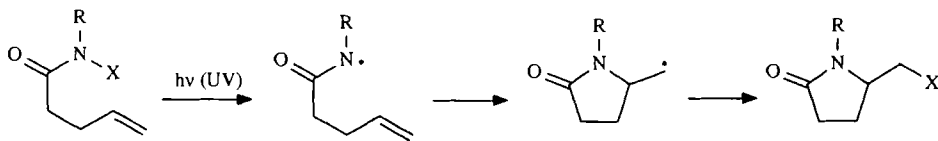
2. Amidyl Radical Cyclizations from *N*-Halo- and *N*-Nitrosamides

Amidyl radicals derived from *N*-halo- and *N*-nitrosoalkenylamides undergo efficient 5-*exo* cyclization in neutral media to form substituted 2-pyrrolidinones and substituted pyrrolidine amides following the radical chain reaction in Scheme 28. Cyclizations in 4-*exo*, 5-*exo*, and 6-*exo* modes occur preferentially to abstraction of a C-5 hydrogen (85CJC2203) even if the position is allylic in some cases. Representative examples of these cyclizations are listed in Table IX. Cyclization of an amidyl radical is generally more favorable with an alkene on the acyl side than on the alkyl side chain (78JOC3746) in contrast to the preference for H-atom abstraction. The cyclization reactions can be complicated by a competing H-atom abstraction sequence that is promoted by the presence of halogen radicals that are formed on initiation, especially Br• (69MI1). This side reaction is quenched and yields of the cyclization reactions are improved by the presence of cuprous ions that scavenge the halogen radicals (78JOC3750).

Much research on amidyl radicals has attempted to assign the ground state configuration of amidyl radicals as to a Σ or Π structure. To date, the results are inconclusive for the class of radicals as a whole. The configuration may be dependent on substituents as is the observed twist angle of the R—N—C—O moiety (81JA624). Electron spin resonance studies by Ingold and co-workers, though they convincingly indicate Π configurations (81JA624), do not correlate with some product studies that suggest an involvement of the Σ configuration in the geometric orientation of some radical cyclizations [78JOC3746; 86JCS(P2)645].

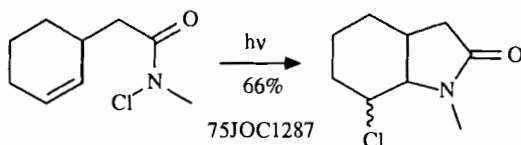
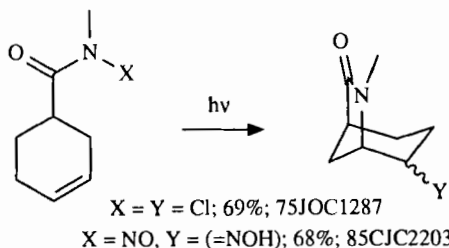
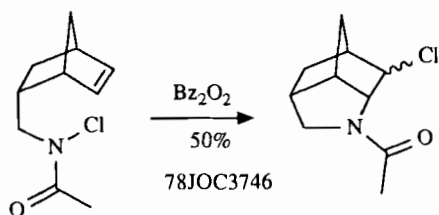
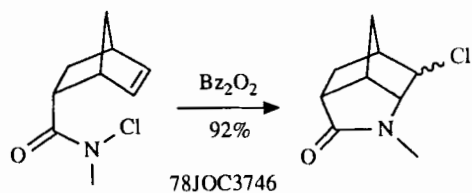
3. Kinetics of Amidyl Radical Cyclizations and H-Atom Abstractions

Absolute rate constants for intramolecular reactions of amidyl radicals have been determined by ESR spectroscopy at low temperature and extrapolated to 27°C (82JA6071). The rate constants for intramolecular 1,5-hydrogen atom abstraction, k_{Abs} , from alkyl and acyl side chains are 1×10^5 and $4 \times 10^4 \text{ s}^{-1}$, respectively. If the C-5 hydrogen on the acyl

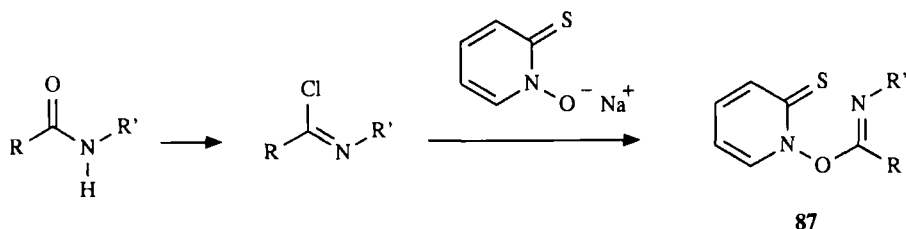


SCHEME 28

TABLE IX
ADDITION PRODUCTS FROM *N*-CHLORO- AND *N*-NITROSOAMIDES



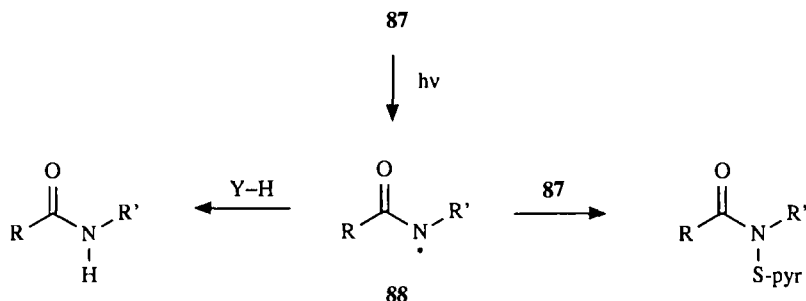
side chain is allylic, $k_{\text{Abs}} = 5 \times 10^6 \text{ s}^{-1}$ at 27°C . The more useful rate constants for synthetic purposes are those for cyclization. The rate of 5-*exo* cyclization, k_r , on the acyl chain is $>1 \times 10^7 \text{ s}^{-1}$ [Eq. (13)], $k_r = 5 \times 10^4 \text{ s}^{-1}$ for 5-*exo* cyclization on the alkyl side chain [Eq. (14)] and $k_r = 1 \times 10^6 \text{ s}^{-1}$ for 6-*exo* cyclization on the acyl chain. However, the ratio of 5-*exo* cyclization on the acyl and alkyl chains does not compare with the results from product studies (91TL1035) and may differ by less



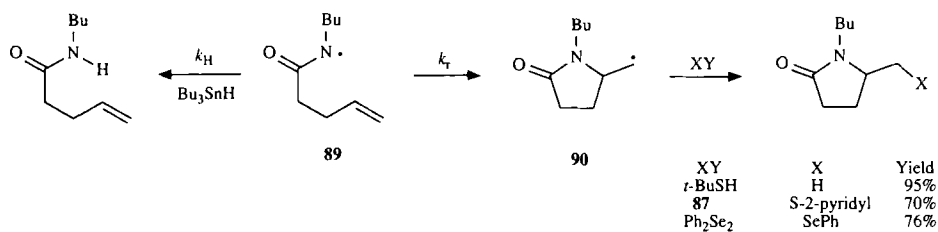
SCHEME 29

xypyridine-2-thione imidate esters undergo efficient 5-*exo* cyclization. Cyclization of the 4-pentenamidyl radical **89** to form carbon radical **90** was competitive with both self-trapping by the precursor and hydrogen trapping by *t*-BuSH on nitrogen (Scheme 31). The rate of trapping of the amidyl radical **89** with Bu_3SnH , k_{H} , is competitive with that of cyclization, k_{r} , and at 25°C ($k_{\text{r}}/k_{\text{H}} = 0.83\text{ M}$ (91TL1035)).

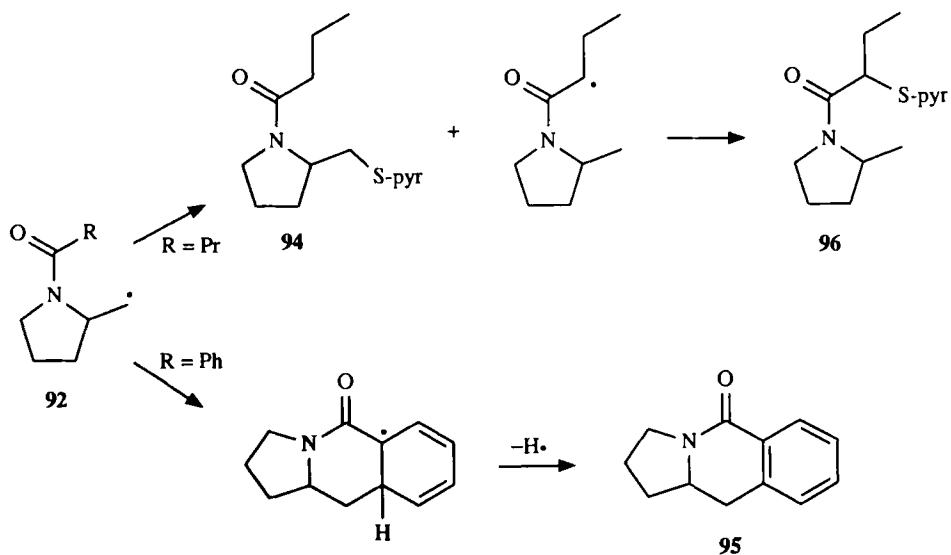
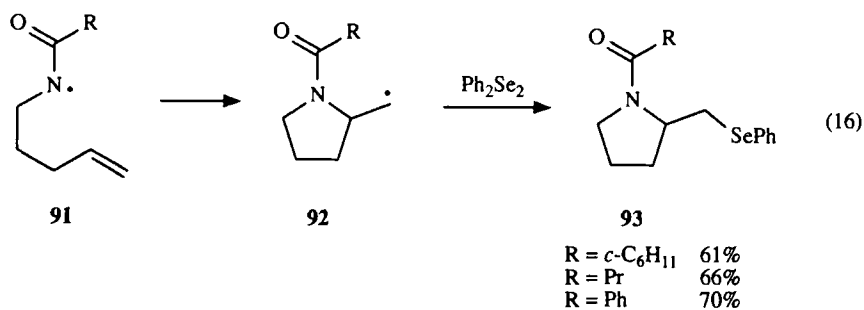
Similar to reactions seen with other PTOC precursors, radical **90** can be trapped efficiently with a variety of radicophiles (X-Y) in good to excellent yields (Scheme 31). Cyclizations onto the acyl side chains appear to be more efficient than cyclizations onto the alkyl side chain but good yields of 2-(phenylselenomethyl)-pyrrolidine amides (**93**) were obtained from cyclized radical **92** when the fast trapping agent Ph_2Se_2 was employed [Eq. (16)]. Under conditions where the carbon radical **92** is trapped at slower rates, $k < 1 \times 10^6\text{ s}^{-1}$, competing reactions occur (Scheme 32). Self-trapping reactions of the butyramidyl radical **92** ($\text{R} = \text{Pr}$) led to the formation of **94** and **96** in a ratio of 1.5 : 1. The product **96** results from a 1,5-radical translocation of **92** that competes with the self-trapping reaction. Similarly, self-trapping or H-atom trapping of the benzamidyl radical **92** ($\text{R} = \text{Ph}$) led to the formation of benzoindolizidinone (**95**) in 47% yield as the only cyclic product obtained (91TL1035).



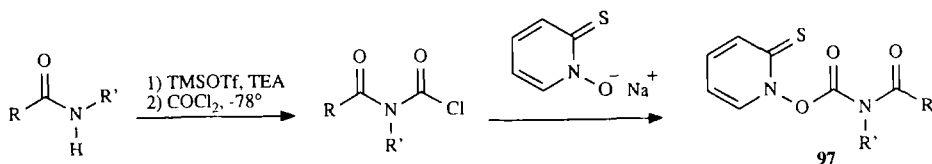
SCHEME 30



SCHEME 31



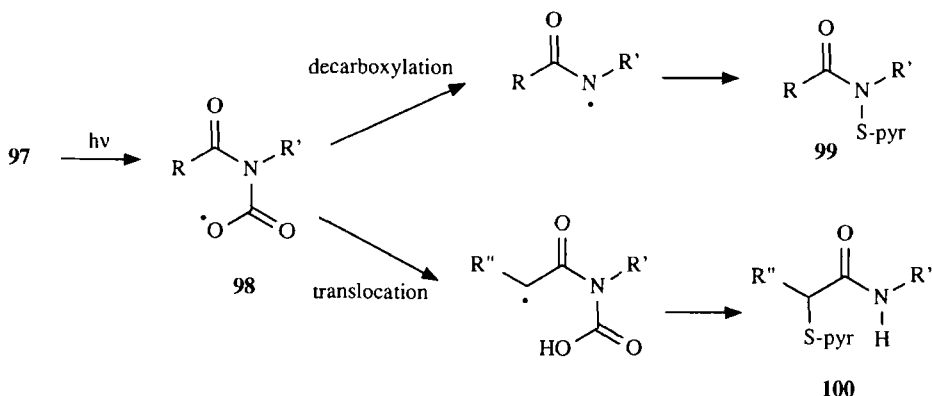
SCHEME 32



SCHEME 33

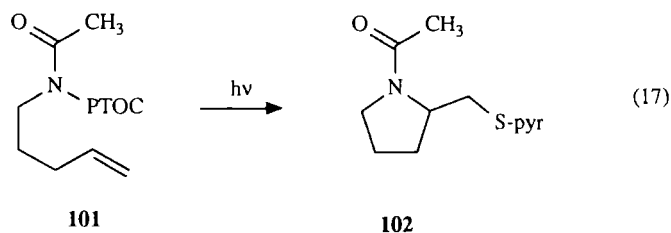
C. AMIDYL RADICALS FROM *N*-ACYL-*N*-ALKYL PTOC CARBAMATES

Recently it has been shown that amidyl radicals can also be generated from *N*-acyl-*N*-alkyl PTOC carbamates (97) (92TL5913). The conditions for the PTOC carbamate preparation are mild (Scheme 33). Visible light irradiation of precursor 97 or radical addition to the thione S atom of 97 initially forms an *N*-acylcarbamoyloxy radical (98) (Scheme 34) analogous to the carbamoyloxy radical from *N,N*-dialkyl PTOC carbamates (Section II,E) except that the rate of decarboxylation of the former apparently is considerably slower than that of the latter. The rate constant for decarboxylation, k_{Dec} , of 98 is small enough that the 1,5 hydrogen atom abstraction, with rate constant k_{Abs} , of a suitably reactive α -hydrogen is competitive with decarboxylation (92TL5913). It is likely that rotation about the amide C—N bond is relatively slow and that the possibility of translocation is determined largely by the conformation around the amide C—N bond of 98 at the instant of formation in addition to radical stabilizing groups at the incipient radical center. The *anti* conformation from which translocation is



SCHEME 34

possible is shown in Scheme 34. In the absence of other reaction pathways, both amidyl radicals and α -amide radicals are trapped by the precursor to generate *N*-(*S*-2-pyridyl)amides **99** and α -(*S*-2-pyridyl)amides **100**. The decarboxylation of **98** to generate amidyl radicals was the predominant pathway when a bidentate Lewis acid, MgBr_2 , was present; apparently the Lewis acid was complexed by the carbonyl groups of **98**, thus giving a *syn* conformation of the carbamoyloxy radical from which translocation was not possible. Decarboxylation also highly predominated in the acetamide derivative and, of course, must occur when no reactive α -hydrogens are present. This method is excellent for the production of acetamidyl radicals, as is indicated by the formation of the substituted pyrrolidine acetamide **102** in 65% yield from the PTOC **101** [Eq. (17)], a substantial improvement in yield over the cyclized acetamidyl radical products obtained in the reaction of an analogous *N*-chloroacetamide (78JOC3750).



VI. Recent Advances

Pyrrolidines and allylic amines have recently been constructed from radical induced cleavage of aziridines. The generation of aminyl radicals from aziridines with β -hydroxy substituents was demonstrated by Murphy (92T1317). Conversion of the β -hydroxy group to an imidazole thiocarbamate and subsequent reaction with Bu_3SnH led to cleavage of the aziridine ring system to generate an aminyl radical. These reactions ultimately gave allylic amines by trapping of the aminyl radical by the tin hydride. The aminyl radicals generated by the route also were shown to undergo $\text{MgBr}_2(\text{Et}_2\text{O})$ promoted cyclization with δ,ϵ -unsaturation to form allylic pyrrolidines.

Neutral aminyl radicals generated from tin hydride-mediated reactions of sulfenamides (Section II,F) have been shown to undergo cyclizations when energetically favored by addition to a strained alkene or by formation of a stabilized intermediate benzylic radical. In both cases, the reverse reaction, cleavage of the β -amino radical, apparently did not occur (92TL4993).

VII. Conclusion

In summary, many of the conditions necessary for the incorporation of nitrogen centered radicals in synthesis have now been met. There now exist several precursors that can be used to generate monoalkyl and dialkyl aminium cation radicals as well as amidyl radicals under relatively mild conditions. An important advance was the extension of Barton's PTOC protocol to the production of various nitrogen centered radicals; the PTOC precursors to nitrogen radicals appear to be as useful as the PTOC ester precursors for carbon radicals, especially in light of the variety of trapping agents available to functionalize the product carbon radicals formed by cyclizations and addition reactions of nitrogen radicals. Relative rate constants for competitive reactions involving nitrogen radicals and, in some cases, absolute rate constants are known; these allow design of efficient nitrogen radical chain reactions. Based on the many ring constructions demonstrated in this review, it is expected that applications of nitrogen radical reactions in synthesis will become more common.

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Tellurium-Containing Heterocycles with Two Heteroatoms

IGOR D. SADEKOV AND VLADIMIR I. MINKIN

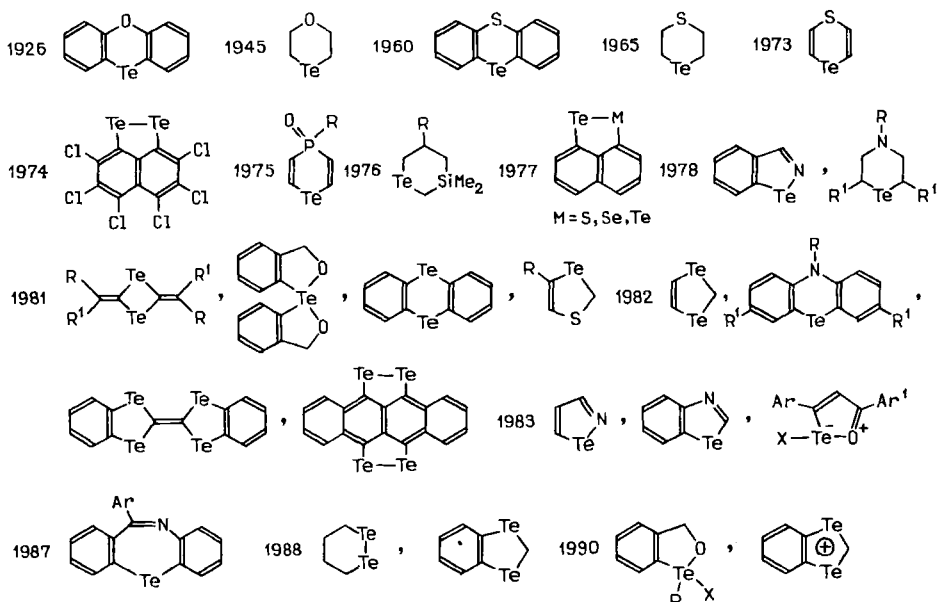
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I. Introduction

The starting point of tellurium organic chemistry dates back to 1840 when the first representative of tellurium-containing organic compounds, diethyl telluride, was synthesized by Woehler (1840LA111). Thus, although the chemistry of tellurium organic compounds dates back more than 150 years, the first tellurium-containing heterocyclic compound, 1-telluracyclo-hexane-3,5-dione (20JCS1456), was prepared only in 1920. The rapid development of organotellurium chemistry in the last decades has been accompanied by an equally rapid expansion of another domain that relates to heterocyclic compounds containing in the ring an additional heteroatom (Si, N, P, O, S, Se). The following sequence of structural types serves to illustrate the chronology of the synthetic discoveries of tellurium-containing heterocycles with two heteroatoms.



The procedures for the preparation of tellurium-containing heterocycles and their reactivity display some characteristic peculiarities in comparison with sulfur and selenium analogs (90M12). These are caused by the specificity of the electronic structure and chemical behavior of the tellurium-containing centers and are characterized by the following salient features.

1. Tellurolate anions possess the highest nucleophilicity in the series of analogous chalcogen derivatives. The same is true for diorganyl tellurides compared to their respective diorganyl sulfides and selenides.

2. Compounds containing dicoordinate tellurium such as diorganyl tellurides and diorganyl ditellurides readily undergo oxidative addition reactions to yield derivatives of tetracoordinate tellurium, the σ -telluranes $B^1R^2TeX_2$ and $RTeX_3$ (X, the electronegative group), which in turn may be reduced to the initial state under mild reaction conditions.

3. The C—Te bonds are the weakest ones in the series of C—Y bonds, where Y is O,S,Se,Te. This provides for their rather facile scission, thus rendering impossible some transformations feasible for their sulfur and selenium analogs.

4. The very strong polarization of the $Te=X \longleftrightarrow Te^+ - X^-$ (X = C,N,O) bonds accounts for the enhanced electrophilicity of the tellurium center in π -telluranes, which markedly exceeds that of other chalcogen centers in respective π -chalcogenuranes (ylides, imides, oxides). Such a polarization provides also for the highest nucleophilicity and basicity of the X-centers in π -telluranes.

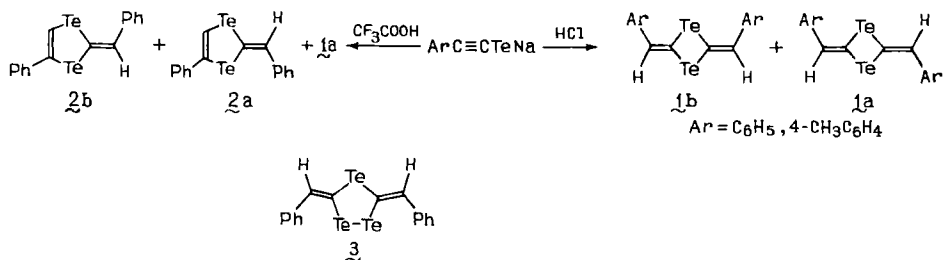
5. σ -Telluranes of types R_2TeX_2 and $RTeX_3$ as well as tetraaryltelluranes Ar_4Te display an enhanced thermal stability in comparison with their sulfur and selenium analogs. The weakness of the C—Te bonds and the tendency of dicoordinate tellurium compounds to undergo oxidative addition reactions frequently impose limitations on the application of the methods used in the chemistry of sulfur and selenium heterocycles to the synthesis of tellurium-containing analogs. Moreover, some of the foregoing properties of telluriumorganic precursors, such as enhanced thermodynamic stability of compounds containing tellurium in higher oxidation states and a very high electrophilicity, e.g., $RTeX_3$, provide for possible novel reaction pathways leading to tellurium heterocycles. A good example is a general approach based on the intramolecular electrophilic cyclization of the corresponding aryl tellurium trichlorides for the preparation of tellurium ring (phenoxatellurine, thiophenoxatellurine, and phenotellurazine) (see Section IV,C), as well as to telluroxanthene (78KGS1567; 80KGS1342) and benzotelluraphene derivatives (71KGS138).

The synthesis and reactions of six-membered (85M16) and five-membered (86M12) tellurium-containing heterocycles have been pre-

viously surveyed, but new knowledge has rapidly accumulated, which requires an updating of the earlier reviews and generalizations.

II. Four-Membered Heterocycles

The first synthesis of four-membered heterocyclic compounds with two tellurium atoms in the ring, 2,4-diarylidene-1,3-ditelluretanes **1** had been accomplished through a treatment of the sodium phenylethynyltelluroate by ethereal HCl, the incorrect structure of five-membered ring compound **2** being first assigned to the product (79ZOK2596). The subsequent detailed study of the reaction product proved it to be a four-membered ring structure (81TL1495; see also 81TL4199, 81ZOK2064). Additionally, the previously unknown *cis*-3,5-dibenzylidene-1,2,4-tritellurole **3** has been revealed to be a by-product of the reaction (81TL4199). Using trifluoroacetic acid as the protonating agent (81CC828) instead of hydrogen chloride causes the reaction to afford a mixture of the *cis*-(**2a**) and *trans*-(**2b**) isomers of 2,6-diphenyl-1,4-ditellura-fulvenes with yields of 5 and 7%, respectively (81CC828). However, in the case of phenylethynylthiolate and selenolate anions, only 2,6-diphenyl-1,4-dithia- and -diselenafulvenes form upon protonation, the yields being 60 and 14%, respectively (67JPR294).



In methylene chloride or DMSO solution in the presence of catalytic amounts of protonic acids (81CC828, 81ZOK2064) or under UV irradiation (81ZOK2064) *cis* isomers **1b** transform into a 1 : 1 mixture of *cis* and *trans* isomers, indicating the expected energy equivalence of **1a** and **1b**. Both of these are characterized by an equal number of shortened intramolecular Te . . . H contacts, which were revealed by an X-ray study of *trans* isomer **1a** (Ar=C₆H₅) (81TL1495) (Fig. 1).

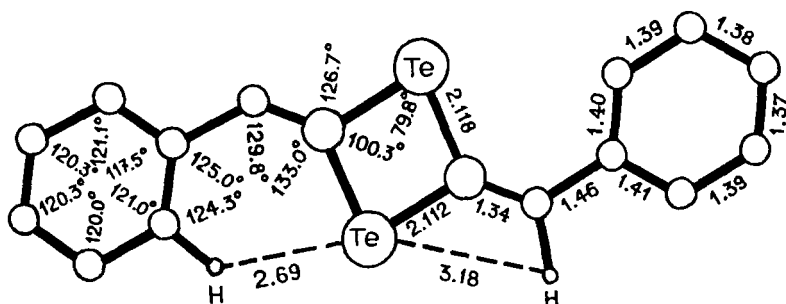


FIG. 1. Bond lengths and angles of *trans*-2,4-benzylidene-1,3-ditellurethane molecule.

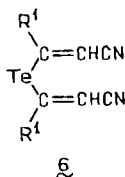
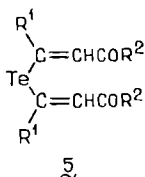
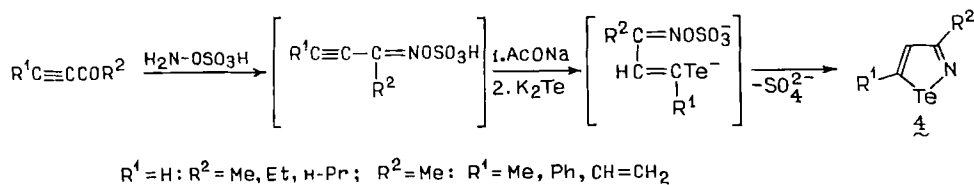
Crystal packing provides evidence of rather strong intermolecular attractive interactions between neighboring molecules that are justified by contracted Te . . . Te distances (3.63 Å), whereas the sum of the Van der Waals radii is 4.40 Å (60M11).

III. Five-Membered Heterocycles

Thus far only eight different types of five-membered heterocycles with two heteroatoms, one of these being tellurium, are known. Of special interest are those containing S, Se, or Te as the second heteroatom in the ring. Such compounds afford electron-donor components of charge-transfer complexes or radical cation salts, exhibiting properties of the so-called organic metals.

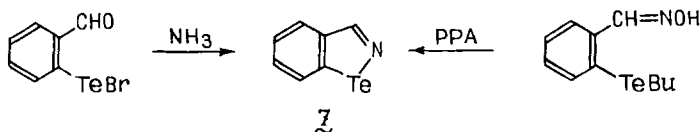
A. ISOTELLURAZOLES

Isotellurazoles **4** were obtained in low yields (3–11%) by the one-pot reaction of alkynyl ketones with hydroxylamino-*O*-sulfonic acid and K₂Te in aqueous solution containing sodium acetate (83S824; 87H1587). A plausible mechanism of the reaction includes formation of the oxime derivative and subsequent nucleophilic addition of telluride anion to the triple bond followed by cyclization to **4**. The reaction is accompanied by the formation of telluro bis(alkenyl ketones) **5** in yields approximately equal to those of **4**. When alkynyl aldehydes are used instead of ketones, the single reaction products are the tellurobis(alkenyl nitriles) **6** (83S824).



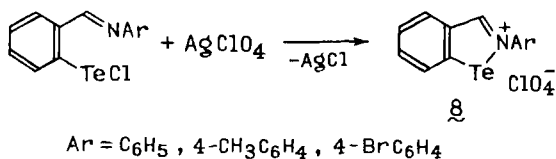
B. BENZOISOTELLURAZOLES

For the synthesis of the parent compound, methods fully analogous to those used for the preparation of benzoisothiazole and benzoisoselenazole have been employed. Benzoisotellurazole **7** was obtained either by coupling of *o*-bromotellurenyl benzaldehyde with ammonia (the yield is 74%) or by the cyclization of the oxime of *o*-butyltellurobenzaldehyde catalyzed by PPA (78JHC865).

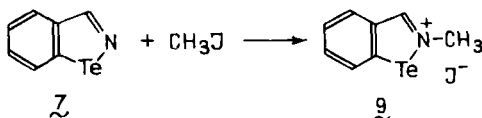


It is worth noting that *o*-bromotellurenyl acetophenone converts upon treatment with ammonia not to 3-methylbenzoisotellurazole, as expected by analogy with the behavior of its selenium analog (73JHC267), but to telluroindoxyl (78JHC865).

The only known derivatives of benzoisotellurazole are the *N*-aryl- and *N*-methylbenzoisotellurazolium salts **8** and **9**. The synthesis of **8** has been accomplished upon treatment of the easily accessible 2-chlorotellurenyl-benzalanilines with an equimolar amount of AgClO_4 [88KGS1426; 90JOM(391)179; 91JOM(402)331]. The yields of this reaction are in the range 65–84%, and thus higher than those for the sulfur and selenium analogs of **8**.



N-Methylisobenzotellurazolium iodide **9** is readily formed when **7** is heated with methyl iodide under conditions similar to those for benzoisothiazole and benzoisoselenazole (78JHC865).



The melting point of benzoisotellurazole **7** (173°C) is anomalously high compared to those of benzoisoselenazole (57°C) and benzoisothiazole (39°C). It has an extremely low solubility in common organic solvents. These properties can be accounted for by the presence of secondary Te . . . N bonds due to drastically shortened intermolecular contacts between molecules in the crystalline state. The length of 2.40 Å (78JHC745) is 1.3 Å less than the sum of the Van der Waals radii of tellurium and nitrogen and very close to the covalent Te—N bond length of 2.11 Å in benzoisotellurazole. No such shortened intermolecular Se . . . N contacts were found in the X-ray studies of benzoisoselenazole (78JHC745). Figure 2 shows the geometric parameters of the benzoisotellurazole molecule.

Among other peculiar properties of benzoisotellurazole (78JHC865) are

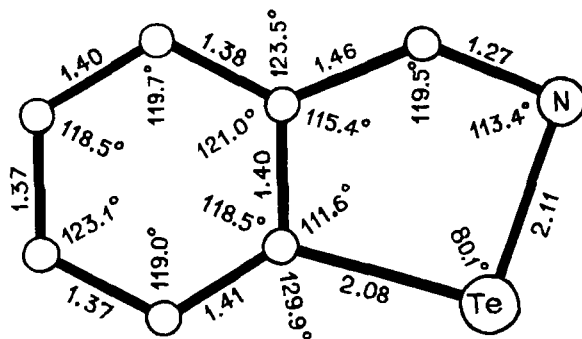


FIG. 2. Bond lengths and angles of benzoisotellurazole molecule.

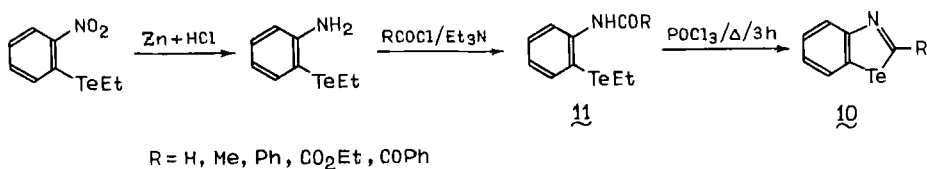
the bathochromic shifts of each of its bands in the UV-absorption spectrum (207, 242, 344 nm) relative to the spectra of benzoisoselenazole (203, 228, 318 nm) and benzoisothiazole (204, 222, 303 nm) as well as the strong deshielding of the H-3 proton manifested by its low-field chemical shift (δ 10.16 ppm, DMSO- d_6). For benzoisoselenazole and benzoisothiazole, chemical shifts of the H-3 protons are δ 9.15 and δ 8.37 ppm respectively.

C. BENZOTELLURAZOLES

The derivatives of 1,3-benzotellurazole have been studied in much more detail than those of its isomer benzoisotellurazole **7**.

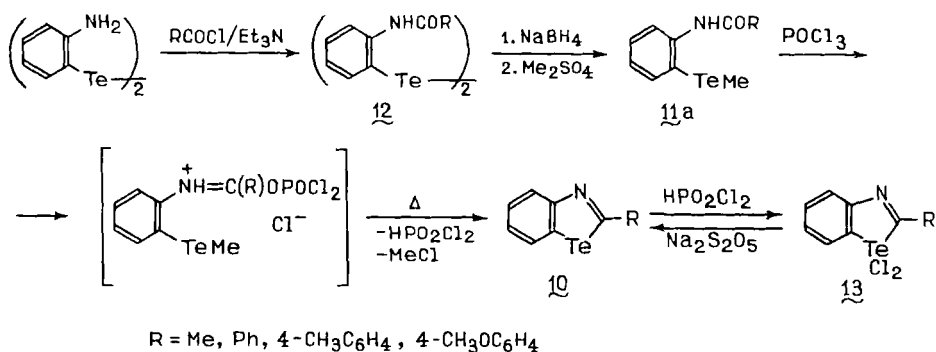
1. Synthesis

Benzotellurazoles **10** were prepared for the first time by a three-step method (83TL5873) with the relatively inaccessible *o*-ethyltelluronitrobenzene (82TL3905) serving as the starting material. The cyclization of the acylanilides **11** to **10** proceeds in 2–15% yields during a 3-h refluxing of their POCl₃ solutions.

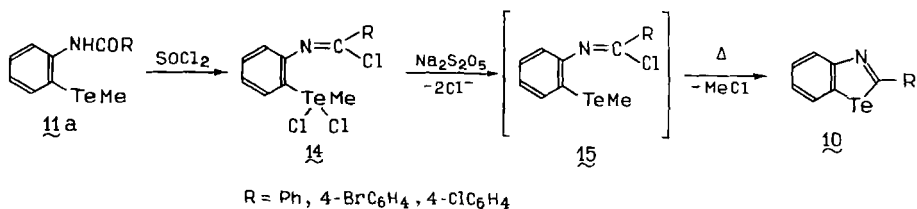


A different approach to acylanilides **11a** involves the reduction of bis(*o*-acylaminophenyl)ditellurides **12** by NaBH₄ and subsequent alkylation of the resultant tellurolate anions with dimethyl sulfate (88KGS276; 89KGS120). The ditellurides **12** in turn were obtained either from the corresponding 2-acylamino-1-chloromercuriarenes (87MI1) or by acylation of bis(*o*-aminophenyl)ditelluride [79JCR(M)1901]. When purified acylanilides **11a** were used in the cyclization reaction and its duration was extended to 6 h, a substantial increase in the yields of the benzotellurazoles (35–65%) resulted (88KGS276; 89KGS120), 1,1-dichlorobenzotellurazoles **13** representing the main component of the reaction product. The entire suggested reaction scheme (89KGS120) is given below.

When thionyl chloride was used instead of POCl₃, the intermediate imidoyl chlorides **14** were isolated in yields higher than 60% (89KGS120). On being reduced in aqueous Na₂S₂O₅ at 60–80°C, they readily eliminate

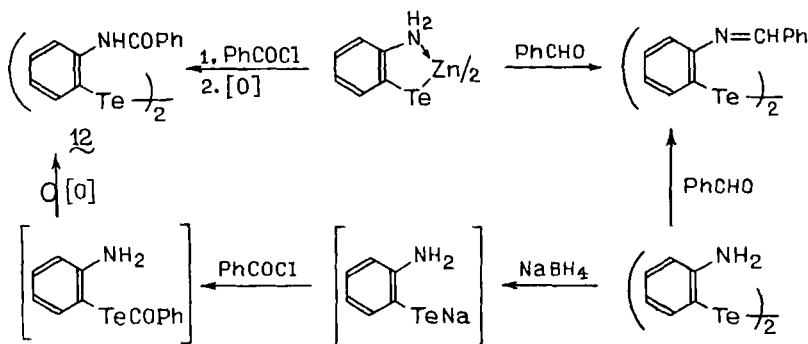


methyl chloride affording benzotellurazoles **10**. Such elimination of methyl chloride from molecules containing the chlorine atom attached to an electron-acceptor group is well known in the syntheses of a number of tellurium-containing heterocycles, e.g., tellurocoumarine (84JHC1281) and telluroisocoumarine (80JOC3535).



Other cyclization agents, e.g., phosphonitrile dichloride, employed in the synthesis of benzothiazoles from *o*-methylthioacetanilides (77S892) proved unsuccessful (88KGS276). Attempts to prepare the benzotellurazole derivatives **10** by reactions similar to those giving rise to other benzochalcogenazoles also failed. No heterocycles **10** have been obtained on attempted coupling of 2-chlorotellurenyl azobenzene with various methylene-active compounds (acetone, acetophenone, malonic acid), whereas 2-chlorosulfonyl azobenzene readily affords benzothiazoles (56JCS648). Another peculiar reaction is that of the zinc or sodium *o*-aminophenyltellurolates (86ZOB2168) with benzaldehyde and its derivatives, unknown for higher chalcogen analogs (89KGS120).

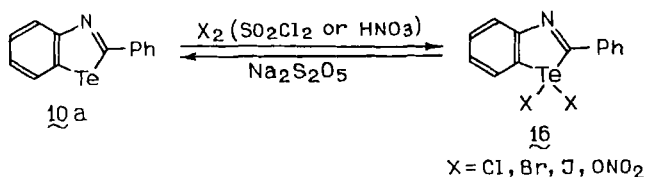
These examples show the specificity of many reactions of organotellurium compounds that thereby prevent the simple extension of synthetic procedures developed for the preparation of sulfur and selenium heterocycles to their tellurium-containing analogs (see also 85MI6; 86MI2).



2. Reactions

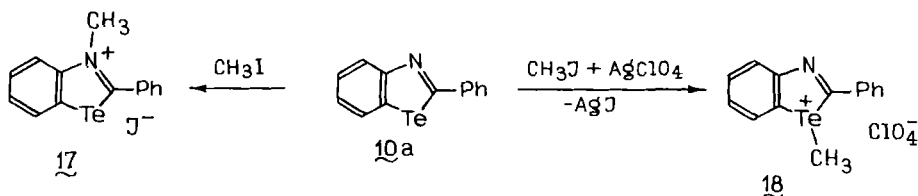
In 1,3-benzazoles (benzoxazoles, benzothiazoles, benzoselenazoles) the heteroatom that is not nitrogen shows very low nucleophilicity and does not serve as a reaction center in electrophilic addition and oxidation–addition reactions. By contrast the tellurium atom in benzotellurazoles is quite susceptible to attack by electrophiles and oxidants.

a. Reactions at the Tellurium Center. 2-Substituted benzotellurazoles readily undergo oxidative addition reactions resulting in the formation of a tetracoordinate tellurium, such a reaction being very typical of diverse two-coordinate tellurium compounds. On treatment with halogens or suluryl chloride 2-phenylbenzotellurazole **10a** converts to its 1,1-dihalogeno derivatives **16** ($X = \text{Cl}, \text{Br}, \text{I}$); nitric acid gives 1,1-dinitrate **16** ($X = \text{ONO}_2$) (89KGS989).

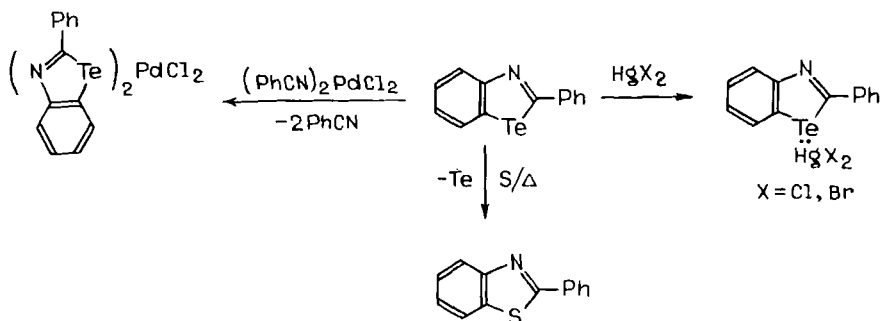


By varying the conditions of the methylation reaction it is possible to prepare both *N*-methyl and Te-methyl derivatives of 2-phenylbenzotellurazole. The iodide of *N*-methyl-2-phenylbenzotellurazole **17** is formed in 91% yield when heated in excess methyl iodide. When an equimolar amount of AgClO_4 is added, the methylation reaction provides the perchlorate of Te-methyl-2-phenylbenzotellurazole **18** in almost quantitative yield (88KGS136; 89KGS989). The reaction represents the first known example of alkylation of a benzochalcogenazole on the chalcogen atom. It is easy

to distinguish between isomers **17** and **18** by the difference in chemical shifts of $N^+ - Me$ (δ 3.81 ppm, CF_3COOH) and $Te^+ - Me$ (δ 2.28 ppm, $DMSO-d_6$) protons.



The soft Lewis acids $Hg(II)$ and $Pd(II)$ readily coordinate to the tellurium atom affording stable molecular complexes of composition 1 : 1 in the case of mercuric salts and 2 : 1 in the case of palladium salts (89KGS989). (Throughout, the number of ligand molecules in a complex is indicated first.) The same composition is characteristic of other coordination compounds of $Hg(II)$ and $Pd(II)$ salts, including the two-coordinate tellurium-containing ligands diaryl tellurides (82CCR133), telluroxanthene (80KGS1342), and phenotellurazine [82DOK(266)1164; 85KGS757].



Since the energy of the $C-S$ bond is higher than that of the $C-Te$ bond, transformation of tellurium-containing heterocycles to their sulfur analogs occurs on substitution of the tellurium center by sulfur, achieved by fusing with elemental sulfur (74MI1; 83MI2). This reaction is also common to benzotellurazoles; the yield in the case of 2-phenylbenzotellurazole is 42% (89KGS989).

b. Reactions at the Nitrogen Center. Apart from the above described N-alkylation reaction (**10a** \rightarrow **17**), protonation of the nitrogen center is known to occur. The basicity of the nitrogen centers in benzoxazoles and benzochalcogenazoles may be compared based on the measurement of

pK_{BH^+} values in acetonitrile solution (91KGS836). These are listed in Table I.

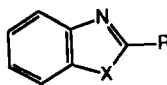
As seen from the data in Table I, the basicity of the nitrogen center steadily grows in the sequence $O < S < Se < Te$ in each of the series of compounds $R = H, Me, Ph$. It was argued that the main electronic factor governing this trend in the basicity constants is the inductive effect of the X centers in the molecules (91KGS836). The values of the inductive constants of the O-, S-, Se-, and Te-containing groups and the electronegativities of these atoms are indeed in parallel with the magnitudes of the pK_{BH^+} constants presented in Table I. Another important factor is the small change in hybridization of the nitrogen atom in the ring on going from benzoxazole to benzotellurazole derivatives. As shown by X-ray crystal studies the CNC angle in the tellurazole ring has its largest value (see Section III,C,3). This indicates the largest s -contribution to the sp^2 -hybrid, which is associated with the growth in the basicity of the lone electron pair (61CRV275).

Reaction constants ρ in the Hammet equation describing the influence of the substituents in the phenyl ring of 2-arylbenzoxazoles, 2-arylbenzothiazoles (68MI2), and 2-arylbenzotellurazoles are approximately the same value, indicating a similar mechanism of expressing the electronic effects of substituents at the nitrogen atom in different benzazoles.

Stable 2-phenylbenzotellurazolium chloride and picrate were isolated as sharply melting crystalline compounds (89KGS989).

c. Aldol Condensation Reactions of 2-Methylbenzotellurazole. The strong polarization of the azomethine bond in the benzotellurazole is

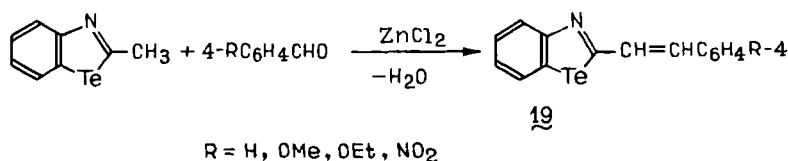
TABLE I
THERMODYNAMIC BASICITY CONSTANTS OF
COMPOUNDS



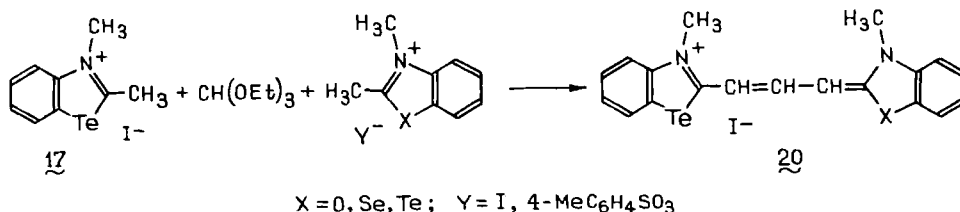
(MeCN, 25°C)

X	R	pK_{BH^+}	X	R	pK_{BH^+}
O	H	5.70	O	Ph	5.95
S	H	7.87	S	Ph	7.24
Se	H	8.03	Se	Ph	7.46
O	Me	7.30	Te	Ph	8.67
S	Me	8.63	Te	4-ClC ₆ H ₄	8.36
Se	Me	8.87	Te	4-BrC ₆ H ₄	8.35
Te	Me	10.10	Te	4-MeC ₆ H ₄	9.20
			Te	4-MeOC ₆ H ₄	9.60

displayed by the pK_{BH^+} values of its derivatives which are the highest in the series of the congeneric benzochalcogenazoles. This facilitates the condensation reactions of the methyl group of 2-methylbenzotellurazole. 2-Styrylbenzotellurazoles **19** were obtained in yields higher than 60% by the condensation of 2-methylbenzotellurazole with various aromatic aldehydes (89KGS120).



A common approach to the synthesis of carbocyanine dyes, treatment of *N*-alkylazolium salts with triethyl orthoformate, has been used to obtain cyanines **20** containing the benzotellurazolium moiety (89KGS120). The long-wave absorption band in **20** is 52 nm bathochromically shifted relative to the corresponding sulfur analog.



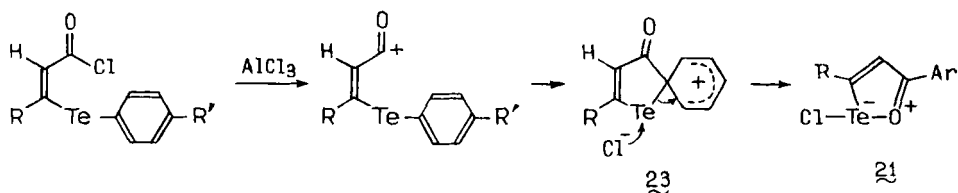
3. Molecular Structure of 2-Phenylbenzotellurazole

Figure 3 shows the bond lengths and the valence angles in 2-phenylbenzotellurazole as defined by an X-ray study (89KGS1690).

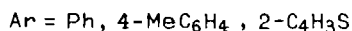
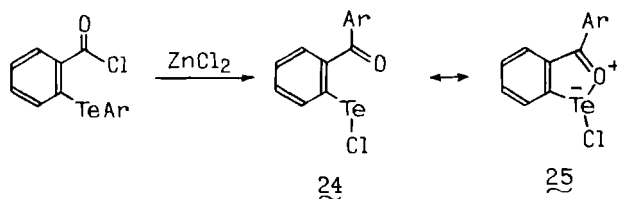
The dihedral angle between the planes of the 2-phenyl ring and the rest of the molecule is 31.2° . The heterocyclic five-membered ring is fully planar but the incorporation into the ring of the bulky tellurium atom results in a significant contraction of the CTeC angle in **10a** as compared to the COC angle in the 1,3-benzoxazole ring [103.8° in the case of 5-nitro-2-cyclohexylaminobenzoxazole (82ZSK163)] and to the CSC angle in the 1,3-thiazole ring (of 2-(2'-hydroxyphenyl)benzothiazole (70ACS3720)). The opposite trend is seen in the magnitude of the CNC angles in the same sequence of compounds: 103.8° , 110.8° , and 116.9° for oxazole, thiazole, and tellurazole rings, respectively.

tion proceeds in boiling CDCl_3 solution with a half-life of 1 h and for **22**, $\text{Ar} = \text{C}_6\text{H}_5$ 30 h. Introduction of the strongly electron-accepting COMe group into the *p*-position of the phenyl ring results in complete inhibition of the reaction. Thus, refluxing **22**, $\text{Ar} = \text{C}_6\text{H}_4\text{COMe-4}$, in CDCl_3 for 72 h provides no change.

The possible reaction mechanism of the successful rearrangements includes intramolecular attack of the electrophilic carbonyl carbon on the aromatic carbon bound to tellurium (ipso-acylation) leading to the spirocyclic α -complex **23**. Subsequent nucleophilic attack of the chloride ion at the tellurium produces 1,2-oxatellurolyl-1-ium chlorides **21**.



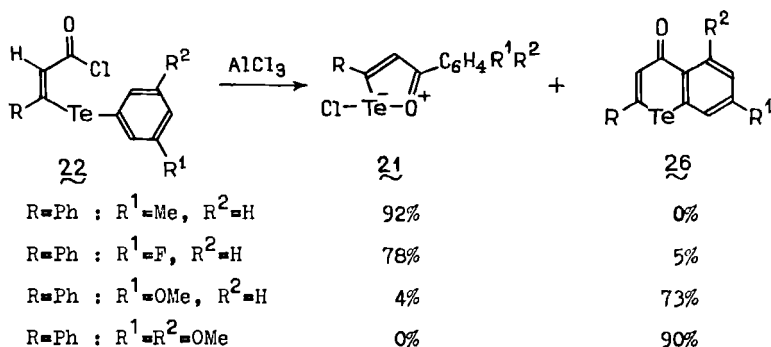
Rearrangement of this type was first observed in the case of *o*-(phenyltelluro)benzoyl chloride by Renson [75CS(A)117; 78T655; 85JOM(287)81], who assigned the product as *o*-chlorotellurenyldiphenyl ketone **24** ($\text{Ar} = \text{C}_6\text{H}_5$). In view of recent evidence for hypervalent $\text{Te}-\text{O}$ bond formation within a molecule by closely disposed tellurium and oxygen atoms, Detty's formulation of the structure of compounds **24** as heterocycles **25** seems to be preferable.



An important difference exists in the direction of cyclization of type **22** β -(arylchalcogeno)propenoyl chlorides as determined by the nature of the chalcogen (83JA883; 88MI2).

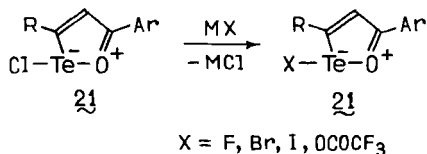
β -(Arylthio)cinnamoyl chlorides are susceptible only to orthoacylation when heated with AlCl_3 to give thioflavones in good yield. The cyclization of β -(arylseleno)propenoyl chlorides under the same conditions proceeds, depending on the nature of the substituents in aryl rings, through either ipso-acylation leading to 1,2-oxaselenolyl-1-ium chlorides or *ortho*-

acylation giving rise to selenoflavones(chromones). In the case of *p*-substituted β -(aryltelluro)propenoyl chlorides, there is no exception to the cyclization reaction to afford 1,2-oxatellurolyl-1-ium chlorides **21**. However, appropriate choice of meta-substituents in the aryl ring that activate the *o*-positions to electrophilic attack and prevent ipso-acylation results in cyclization with predominant formation of tellurochromones (flavones) **26** as exemplified by the scheme below.



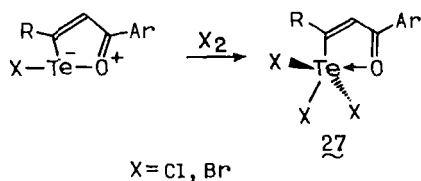
2. Reactions

The presence of a hypervalent Te—O bond that is part of the three center—four electron bond (3c—4e) in the linear Cl—Te—O fragment does not markedly affect the reactivity of the 1,2-oxatellurolyl-1-ium chlorides **21**, **25**, which behave as expected of true tellurenyl halides. Thus, on treatment of **21** with LiBr, NaI, and CF₃COOAg (83JA875) substitution of chloride by bromide, iodide, or trifluoroacetate is readily achieved. When AgBF₄ is used 1,2-oxatellurolyl-1-ium fluorides are obtained.

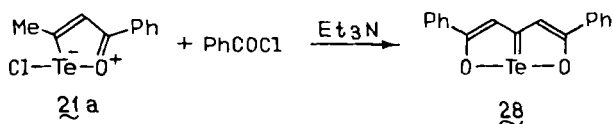


The oxidative addition of chlorine and bromine to the 1,2-oxatellurolyl-1-ium halides **21** leads to the trihalogenides **27** (86JOC1692) under rather mild conditions. When the 1,2-oxatellurolyl-1-ium chloride is treated with bromine, or the bromide is treated with chlorine, no compounds with different halogen atoms attached to the tetracoordinate tellurium are obtained. The reaction products consist of mixtures of trichloride **27** (X = Cl) and tribromide **27** (X = Br). However, treatment of

1,2-oxatellurolyl-1-ium iodides with iodine leaves the initial heterocyclic compounds unchanged.

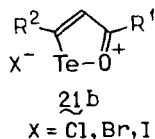


By coupling 1,2-oxatellurolyl-1-ium chloride **21a** with benzoyl chloride in the presence of Et_3N , the diphenyl derivative of a novel heterocyclic system dioxatellurapentalene **28** was synthesized in 40% yield (83JOC5149). Its structure was proved by X-ray diffraction.



3. Molecular Structure

Reactions of the 1,2-oxatellurolyl-1-ium halides **21** bear witness to a highly ionic character of the $Te-X$ ($X = Cl, Br$) bonds, evidence of their salt-like structure **21b**.



However, an X-ray crystal study of one of the derivatives of **21**, 3-phenyl-5-(4-methoxyphenyl)-1,2-oxatellurolyl-1-ium chloride **21** ($R = Ph$, $Ar = C_6H_4OMe-4$) justifies its T-shaped tricoordinate tellurium structure (83JA875), which is portrayed in Fig. 4.

As seen from Fig. 4, the $Cl-Te-O$ angle is very close to 180° , thus indicating a linear arrangement of these centers typical of 3c-4e hyper-valent bonding. Since the tellurium atom in **21** is involved in intramolecular coordination it does not form additional secondary intermolecular $Te \cdots Cl$ bonds in the crystal.

An X-ray crystal structure study of the bromine adduct of 3,5-diphenyl-1,2-oxatellurolyl-1-ium bromide **27** has also been reported (86JOC1692). The bond lengths and valence angles within the five-membered ring in **27**

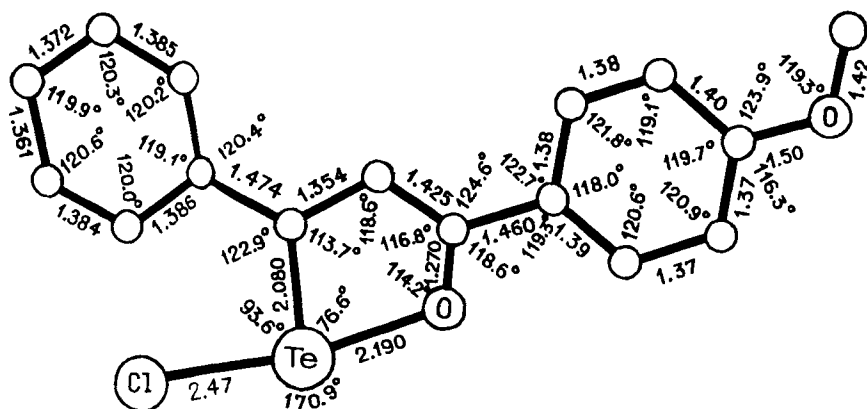


FIG. 4. Bond lengths and angles of chloride 3-phenyl-5-(4-methoxyphenyl)-1,2-oxatellurolyl-1-ium molecule.

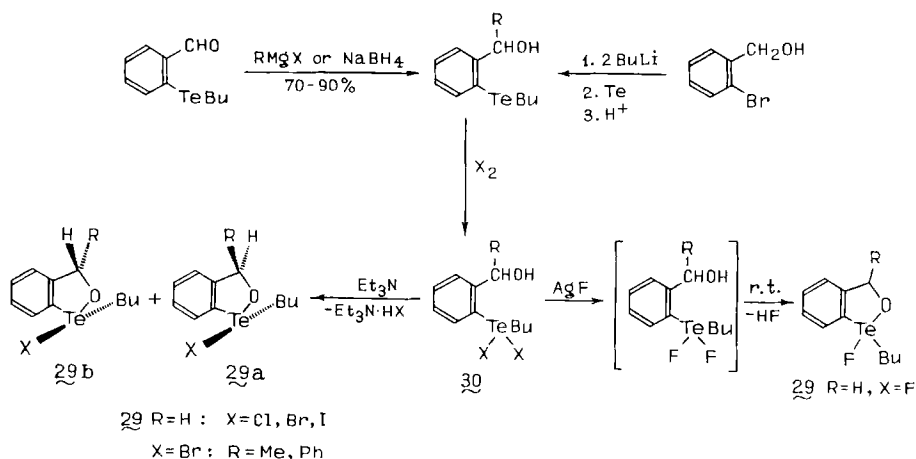
and its precursor **21** are close. The coordination of the tellurium in **27** is as expected, a slightly distorted trigonal bipyramid.

E. 3*H*-BENZOXATELLUROLES-2,1

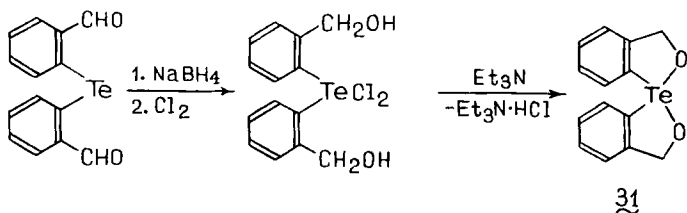
To date only the tetracoordinate tellurium derivatives of this heterocycle, 1-halogeno-1-butyl-3-*R*-benzoxatelluroles-2,1 **29**, are known. These have been prepared in three steps starting from 2-butyrtellurobenzaldehyde (90ZOB471; 91UPI), as shown in the scheme. The key step is the dehydrohalogenation of the intermediate products **30**; the conditions for this reaction are defined by the nature of halogen attached to the tellurium. In the case of 2-butyldifluorotellurobenzylic alcohol **30** ($X = F$) that is prepared *in situ* in acetone upon treatment of **30** ($X = Br$) with AgF , cyclization to **29** occurs spontaneously. The dichloro derivative **30** ($X = Cl$) converts to **29** ($X = Cl$) by passing its solution in chloroform through an Al_2O_3 column. In the case of dibromide **30** ($X = Br$) or diiodide **30** ($X = I$), it becomes necessary to apply a strong base, Et_3N , as cyclizing agent (91UPI).

In the case of benzoxatelluroles **29** ($X = Br$) having in the 3-position either a methyl or a phenyl substituent, a mixture of two diastereomers **29a** and **29b** is formed.

A similar approach has been used previously in the synthesis of the derivative of 3*H*-benzoxatellurole-2,1 containing a spirocyclic tetracoordinate tellurium center, 1,1-spiro[3*H*-benzoxatellurole-2,1] **31** (81KGS122).



The heterocyclic compound **31** was obtained in 98% yield upon treatment of bis(2-hydroxymethylphenyl)tellurium dichloride with Et_3N in benzene.

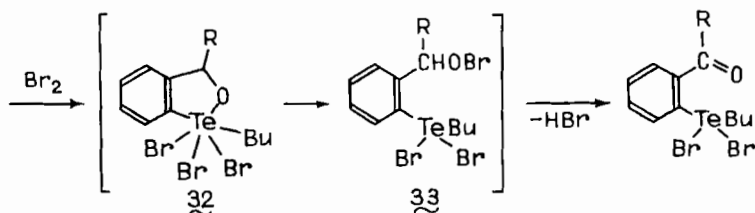


By contrast to its spiro sulfurane analog, **31** in a CDCl_3 and nitrobenzene solution at room temperature displays a rapid polytopal rearrangement that results in the averaging of the diastereotopic protons of the methylene groups. The increase in the frequency of the polytopal rearrangements on going from sulfuranes to telluranes is in accord with theoretical predictions (77ZOB2011).

By contrast with the structurally congeneric telluronium salts $\text{R}_3\text{Te}^+\text{X}^-$ that readily eliminate alkyl or aryl halides RX upon heating either in the solid or in pyridine solution (74MI1; 83MI2), benzoxatelluroles **29** exhibit enhanced thermal stability and do not eliminate butyl halides even under prolonged heating.

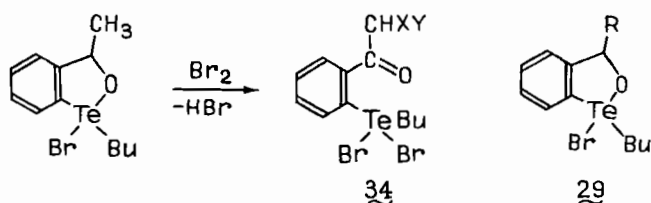
Compounds **29** ($\text{X} = \text{Br}$) smoothly undergo halide exchange reactions (with F^- , CH_3COO^-) and react with bromine through $\text{Te}-\text{O}$ bond cleavage to give, depending on the nature of the substituents in the position 3 of the heterocyclic fragment, either aldehydes or ketones bearing the $\text{Te}(\text{Bu})\text{Br}_2$ substituent in the o -position of the benzene ring. The reaction

proceeds most probably through the intermediacy of the six-coordinate tellurium heterocyclic compound **32**, which rearranges to **33**. The yields are in the range 70–90% (90ZOB471; 91UPI).



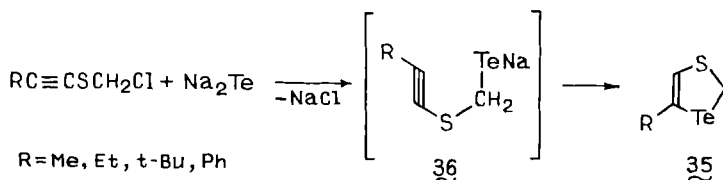
Taking into account that benzoxatelluroles **29** with the substituent R in the five-membered ring are prepared from 2-butyltellurobenzaldehyde, the reaction considered above may be regarded as a new preparative method for the conversions of *o*-alkyltellurobenzaldehydes into their respective ketones and of *o*-alkyltellurobenzylic alcohols into aldehydes. Attempts to oxidize 1-(*o*-methyltellurophenyl)ethanol-1 into *o*-alkyltelluroacetophenone failed (71B5B669).

When the 3-methyl derivative of **29** is exposed to bromination, the reaction does not end with the formation of the acetophenone derivative **34** (X = Y = H), but gives rise to products of further bromination, *o*-butyldibromotelluro- α -bromoacetophenone **34** (X = H, Y = Br) and *o*-butyldibromotelluro- α,α -dibromoacetophenone **34** (X = Y = Br) (91-UPI).



F. 1,3-THIATELLUROLES

A few representatives of this heterocyclic system **35** were synthesized in very high yield (85–90%) by the intramolecular nucleophilic cyclization of the acetylene derivatives **36** (81RTC10), which in turn were obtained by treatment of alkynyl(chloromethyl) sulfides with one equivalent of Na_2Te , the latter being prepared from elemental sodium and tellurium in liquid ammonia.

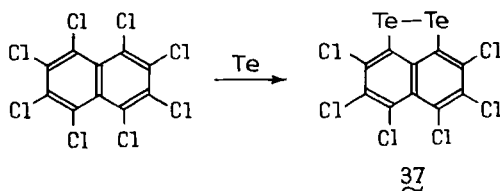


G. 1,2-DITELLUROLES

Of 1,2-ditellurole derivatives only peri-bridged compounds containing the naphtho[1,8-*cd*] moiety attached to CC bonds in the five-membered tellurium-containing heterocycle have been described to date. Although the synthesis of 3-benzylidene-4-phenyl-1,2-ditellurole has been reported (15% yield) through coupling phenacetylene with elemental tellurium in the superbasic system of KOH-HMPTA-SnCl₂-H₂O (85M15; 86ZOK220), it was later found that in fact the product of this reaction is a mixture of stereoisomers of 2,6-diphenyl-1,4-ditellurafulvenes (89TL441).

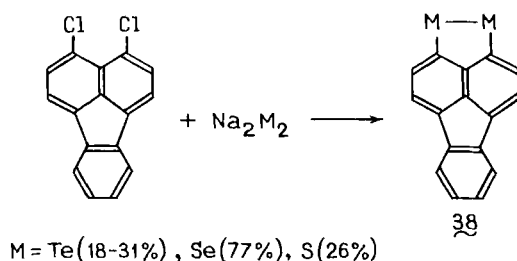
1. Synthesis

The first representative of the 1,2-ditelluroles, 3,4,5,6,7,8-hexachloronaphtho[1,8-*cd*]1,2-ditellurole **37**, was obtained in low yield by heating octachloronaphthalene with elemental tellurium at 350°C (73USP3769276) by analogy with the method developed for the synthesis of congeneric 1,2-dithiole and 1,2-diselenole derivatives (72T963).

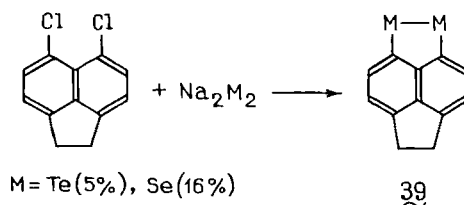


In general two principal approaches have been employed for the synthesis of the 1,2-ditelluroles hitherto described: (a) nucleophilic substitution of the halogens in the peri-positions of the naphthalene fragment by the Te₂²⁻ dianion and (b) interaction of the 1,8-dilithionaphthalene derivative with elemental tellurium followed by hydrolysis and spontaneous oxidation of the intermediates with air. As usual, sodium ditelluride is prepared from elemental sodium and tellurium in such dipolar solvents as HMPTA or DMF, which also serve as media for carrying out the reaction with dihalogen derivatives. Thus a series of fluoroantheno[3,4-

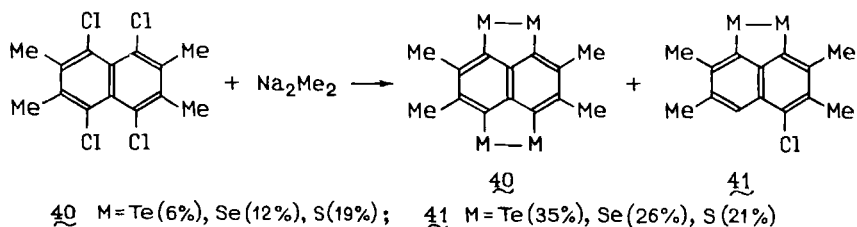
cd][1,2]dichalcogenoles **38** (M = Te, S, and Se) were prepared starting from 3,4-dichlorofluoroanthene (86TL2011; 87M15).



The same procedure was applied to the synthesis of 5,6-dihydroacenaphtho[5,6-*cd*][1,2]ditellurole and diselenole **39** (88BCJ2013).

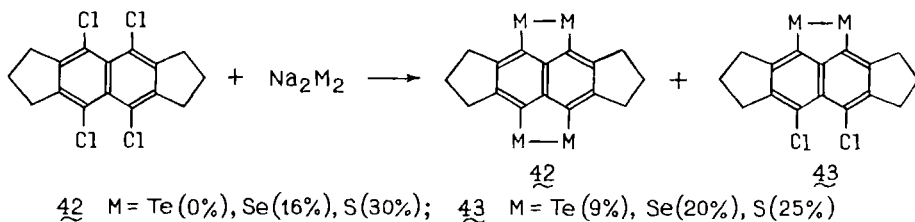


Also, ditelluroles **40** (M = Te) and similar dichalcogenoles (M = S, Se) containing two identical dichalcogenide bridges within a molecule have been obtained by nucleophilic substitution of the chlorines in the peri-positions of 1,4,5,8-tetrachloro-2,3,6,7-tetramethyl-naphthalene by dichalcogenide dianions (87CL315; 88M18). 1,8-Dichalcogena-4-chloro-2,3,6,7-tetramethyl-naphthalenes **41** were isolated as attendant products. As the yields of **40** and **41** shown in the scheme below indicate, the balance between these two is gradually shifted in favor of **41** on going from disulfides to ditellurides.

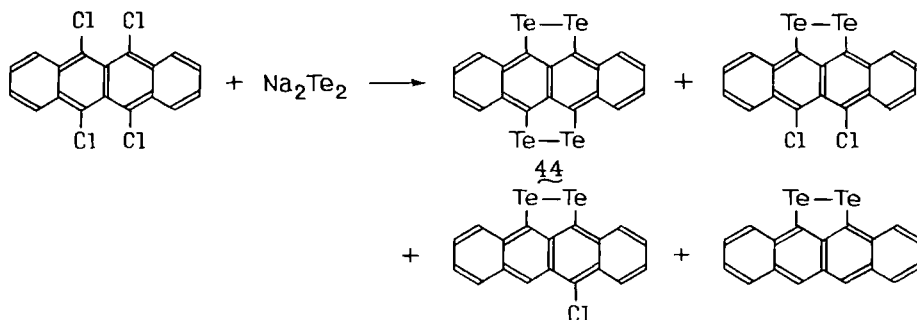


Interestingly, when 2,3;6,7-bis(trimethylene)naphthalene is treated with sodium ditelluride in HMPTA or 1,3-dimethyl-2-imidazolidinone solution,

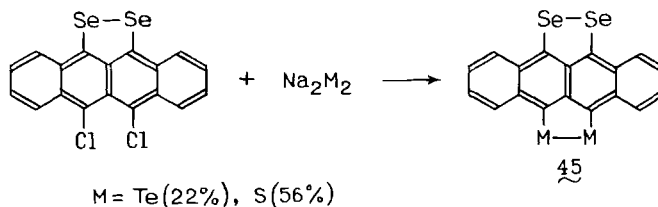
no tetratelluranaphthalene **42** ($M = \text{Te}$) is observed at all, the only product being represented by 1,8-ditellura-4,5-dichloro-2,3,6,7-bis(trimethylene)naphthalene **43** (88MI8).



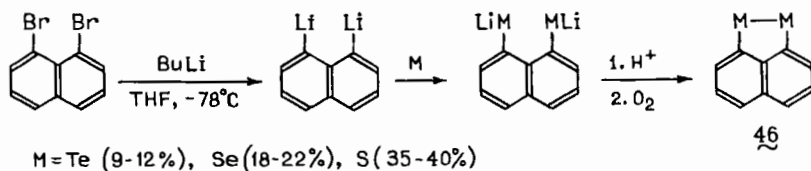
Because of the very strong reducing properties of the ditelluride dianion, its reaction with 5,6,11,12-tetrachlorotetracene results, along with tetratelluratetracene **44** (yield 20%), in the formation of products of a partial reduction of the tetrachlorotetracene (82MI3).



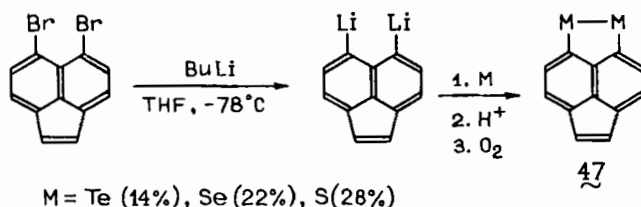
The reaction of the peri-dichalcogenoaromatics with dichalcogenide dianions was also used in the synthesis of various mixed tetrachalcogenatetracenes **45** (84ZOK891).



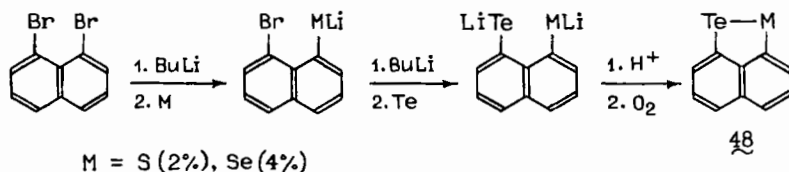
The second approach to the synthesis of peri-bridged dichalcogenoles was applied for the first time to the preparation of naphtho[1,8-*cd*][1,2]-dichalcogenoles **46**, obtained in low yields according to the scheme below (77JA255; 78ANY382).



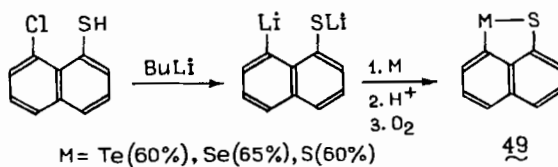
The same sequence of the reactions was employed also in synthesis of acenaphtho[5,6-*cd*][1,2]dichalcogenoles **47** (80TL4565).



1,8-Dilithionaphthalene serves as a starting material for the synthesis of the mixed 1,2-dichalcogenoles **48** (77JA7743; 78ANY382). The yields of **48** are extremely low because of competing reactions with each of the chalcogenes resulting in a formation of a mixture of symmetric 1,2-dichalcogenoles.



More productive is an approach to the synthesis of mixed 1,2-dichalcogenoles **48** founded on the reaction of 1-chloro-8-mercaptanaphthalene (77JA7743; 78ANY382). The yields of 1-thia-8-chalcogenanaphthalenes **49** amount to 44-65%.

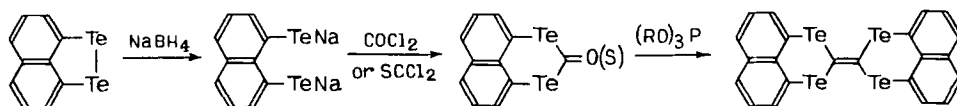


2. Reactions

Not counting the data on the complexation reactions of 1,2-ditelluroles (Section III,G.3), information about their reactivity is very scarce. The interaction of the dichalcogenoles **46** with methyl lithium followed by alkylation has been studied (77JA255). In the case of the dithiole, the single product is 1,8-bis(methylthio)naphthalene, the diselenole affords a mixture of 1,8-bis(methylseleno)naphthalene and 1-methylseleno-8-methylnaphthalene, whereas the reaction with the ditellurole produces no organotellurium compounds, giving rise instead to 1,8-dimethylnaphthalene and trace amounts of perylene. The latter finding has an explanation in that organolithium and organomagnesium compounds can cleave both Te—Te (63CB247) and C—Te (87AG1221) bonds.

Due to the fact that the naphtho[1,8-*cd*][1,2]dichalcogenoles possess very low first ionization potentials (7.03–7.14 eV), they are susceptible to oxidation to give radical cations, $\text{AlCl}_3/\text{CH}_2\text{Cl}_2$ being a convenient oxidative system (81CB2662). In contrast with its sulfur and selenium analogs the radical cation obtained from the naphtho[1,8-*cd*][1,2]ditellurole does not show a well-resolved ESR spectrum in solution even at temperatures as low as 200 K.

No reactions of 1,2-ditelluroles characteristic of ditellurides such as oxidative addition of halogenes, reduction of the Te—Te bond, or conversion to telluronium salts by alkylation have been studied. The general interest in bridged 1,2-ditelluroles lies in their use as components of charge-transfer complexes and radical ion salts exhibiting metal-like electric conductivity. However, a number of conceivable approaches to promising organic-metal-type compounds involve exactly the above-mentioned reactions of bridged 1,2-ditelluroles, for example



3. Charge-Transfer Complexes and Radical Cation Salts of 1,2-Dichalcogenoles

Data on the UV-absorption spectra and the polarographic oxidation potentials of some 1,2-ditelluroles and its analogs are listed in Table II.

As expected on going from sulfur to the corresponding tellurium-containing compounds, an increase is observed in the electron-donor prop-

TABLE II
UV ABSORPTION SPECTRA AND OXIDATION POTENTIALS OF
1,2-DICHALCOGENOLES **38**, **39**, **40**, **45**, **46**

Compound	UV spectra			Reference
	Solvent	λ_{\max} (nm)	$E_{1/2}$, V	
Fluorantheno[3,4- <i>cd</i>][1,2]ditellurole 38	CS ₂	503, 719 sh	+0.53 ^c	86TL2011; 88BCJ2013
Fluorantheno[3,4- <i>cd</i>][1,2]diselenole 38	CS ₂	442,466,540 sh	+0.88 ^c	86TL2011; 88BCJ2013
Fluorantheno[3,4- <i>cd</i>][1,2]dithiole 38	CS ₂	438,461,500 sh	+1.15 ^c	86TL2011; 88BCJ2013
5,6-Dihydroacenaphto[5,6- <i>cd</i>][1,2]ditellurole 39	—	—	+0.32 ^b	88BCJ2013
5,6-Dihydroacenaphto[5,6- <i>cd</i>][1,2]diselenole 39	—	—	+0.57 ^b	88BCJ2013
5,6-Dihydroacenaphto[5,6- <i>cd</i>][1,2]dithiole 39	—	—	+0.68 ^b	88BCJ2013
1,8;4,5-Bis(ditellura)-2,3,6,7-tetramethylnaphtalene 40	CHCl ₃	281,445,647,1028	+0.31, +0.72 ^c	87CL315
1,8;4,5-Bis(diselena)-2,3,6,7-tetramethylnaphtalene 40	CHCl ₃	267,416,528,855	+0.46, +0.90 ^c	87CL315
1,8;4,5-Bis(dithia)-2,3,6,7-tetramethylnaphtalene 40	CHCl ₃	261,408,500 sh 700	+0.48, +0.95 ^c	87CL315
5,6-Diselena-11,12-ditelluratetracene 45	DMF	465,670,730	—	84ZOK891
5,6-Diselena-11,12-dithiatetracene 45	DMF	465,658,711	—	84ZOK891
Naphtho[1,8- <i>cd</i>][1,2]ditellurole 46	c-C ₆ H ₁₂	257,267,383 sh 410	+0.45 ^a +0.43 ^b	77JA255; 78ANY382 87M15; 88BCJ2013
Naphtho[1,8- <i>cd</i>][1,2]diselenole 46	c-C ₆ H ₁₂	212,255 sh,262 367 sh,380	+0.76 ^a +0.77 ^b	77JA255; 78ANY382 87M15; 88BCJ2013
Naphtho[1,8- <i>cd</i>][1,2]-dithiole 46			+0.86 ^a +0.94 ^b	77JA255; 78ANY382 87M15; 88BCJ2013

Note. The values of $E_{1/2}$ are obtained in ^aMeCN, ^bCH₂Cl₂, ^cPhCN.

erties of the dichalcogenoles. Annulation of an additional benzene ring to **46** results in a lowering of the electron-donor ability of the fluoroanthene (peri-annulation) and acenaphthene (lateral annelation) derivatives **38** and **47**, respectively.

1,2-Ditelluroles **39** (88BCJ2013), **40** (87CL315; 88MI8), **46** (77JA255; 78ANY382), **47** (80TL4565), and **48** (77JA7743) readily form with tetracyanoquinodimethane (TCNQ), its tetrafluoro derivative and with I_2 charge-transfer complexes when components are allowed to interact in solution. Some exceptions are the charge-transfer complex of **47** with TCNQ that has a very low solubility at room temperature (80TL4565) and the inhibition of the reaction between TCNQ and the 1,2-ditellurole **38** by the extreme insolubility of the latter in organic solvents (86TL-2011; 87MI5). Among the ditellurole-TCNQ charge-transfer complexes the highest electric conductivity is displayed by those containing 5,6-dihydroacenaphtho[5,6-*cd*][1,2]ditellurole **39** [$1.8 \times 10^{-1} \text{ ohm}^{-1}\text{cm}^{-1}$ (88BCJ2013)] and naphtho[1,8-*cd*][1,2]ditelluroles **46** [$2 \cdot 10^{-2} \text{ ohm}^{-1}\text{cm}^{-1}$ (77JA255; 78ANY382)] as the donor components. The conductivity increases in the sequence S—Se—Te for the TCNQ complexes of the dichalcogenoles **39** (10^{-8} , 10^{-5} , and $1.8 \times 10^{-1} \text{ ohm}^{-1}\text{cm}^{-1}$) and **46** (10^{-11} , 5×10^{-8} and $2 \times 10^{-2} \text{ ohm}^{-1}\text{cm}^{-1}$, respectively). At the same time for the TCNQ complexes of 1,4,5,8-tetrachalcogena-2,3,6,7-tetramethylnaphthalenes **40** no substantial influence of the nature of the chalcogene on the electric conductivity was observed (87CL315; 88MI8), all the values lying around $10^{-3} \text{ ohm}^{-1}\text{cm}^{-1}$:

Perchlorates of the radical cations **38** (87MI5) and iodides of the radical cations **40** (88MI8) were prepared by electrochemical oxidation, whereas the salts of the tetratelluratetracene radical cation $(\text{TTeT})_2\text{X}$ were formed through its oxidation by CuX_2 ($\text{X} = \text{Cl}, \text{Br}$) in DMF solution (81IZV1432). The electric conductivity of the latter as well as that of their selenium analogs achieves values of $1\text{--}2 \text{ ohm}^{-1}\text{cm}^{-1}$.

4. Molecular Structure

The molecular geometry of the tetratelluratetracene **44** determined by an X-ray diffraction study (81CSC663; 82MI2) is shown in Fig. 5.

The planar molecules in the crystal are stacked in layers, the neighboring ones being connected by secondary $\text{Te} \cdots \text{Te}$ bonds (3.70 Å). These distances are 0.7 Å shorter than the sum of the tellurium Van der Waals radii.

H. 1,3-DITELLUROLES

1. Synthesis

Based on the extremely high nucleophilicity of the telluroate anions, a general approach to the synthesis of the 1,3-ditelluroles **50** was developed (82TL1531) that involves the following sequence of reactions.

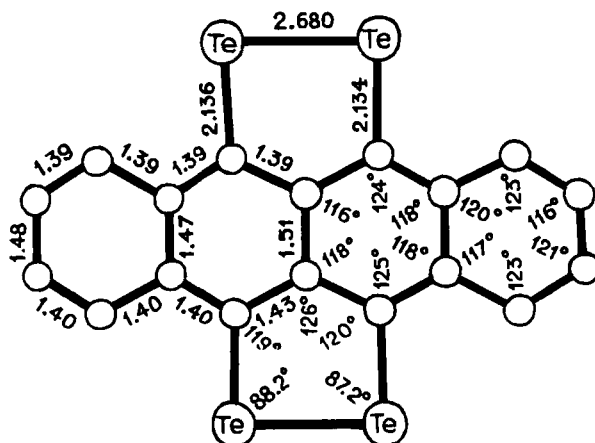
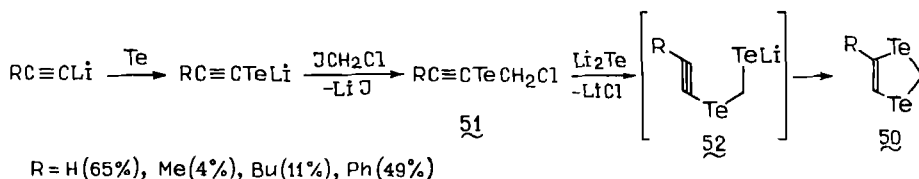


FIG. 5. Bond lengths and angles of tetratelluratetracene molecule.



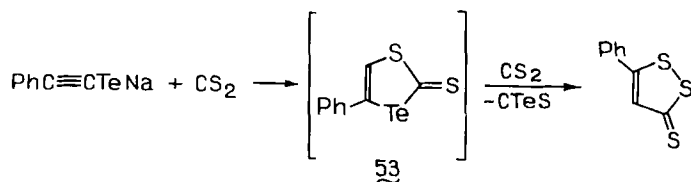
The key step is the intramolecular cyclization of the intermediate telluroate anions **52** formed by treatment of compounds **51** with equimolar amounts of Li_2Te . The by-products of the reactions are the tellurides $(\text{RC}\equiv\text{CTe})_2\text{CH}_2$. The yields of the ditelluroles **50** are strongly affected by the substituents at the triple bond and lie in the range 4–65%. The method is similar to that suggested earlier for the synthesis of the 1,3-thiatelluroles (81RTC10).

Of derivatives of the 1,3-ditelluroles, only the ditellurafulvenes **2** are known. Their first representatives, *cis*- and *trans*-2,6-diphenyl-1,4-ditellurafulvenes **2** were obtained in 12% total yield along with *trans*-2,4-benzylidene-1,3-ditellurethane **1a** when sodium phenylethynyltelluroate was treated with trifluoroacetic acid in ether (81CC828) (see Section II).

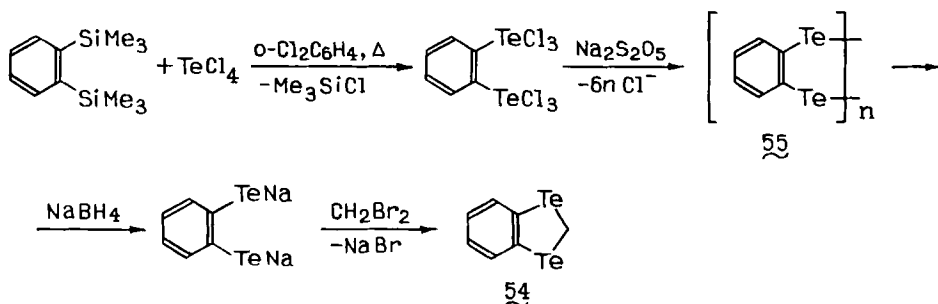
The synthesis of compounds **2a**, **2b** may be realized as a one-pot reaction of phenylacetylene with powdered tellurium in the superbasic medium ($\text{KOH-HMPTA-SnCl}_2\text{-H}_2\text{O}$) (89TL441). The yield of the mixture of *trans*- and *cis*-isomers is 15%.

As noted in the Introduction, methods derived for the synthesis of 1,3-dithioles and 1,3-diselenoles failed when applied to the preparation of

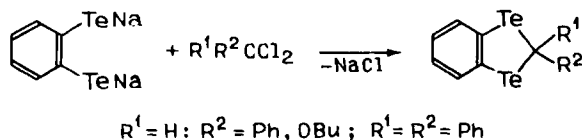
1,3-ditelluroles. Thus, coupling sodium phenylethynyltelluroate with CS_2 leads to, instead of 1,3-thiatellurole-2-thione **53**, whose formation might be anticipated by analogy with the reaction of sodium phenylethynylthiolate (67JPR294), the 5-phenyl-1,2-dithiole-3-thione (81ZOK2064).



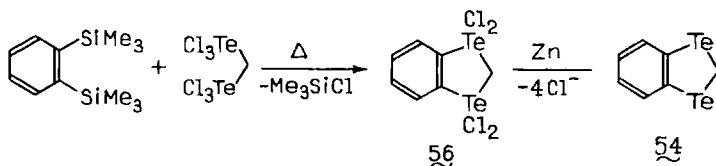
Benzo-1,3-ditellurole **54** was prepared in 40–47% yield by reacting dibromomethane with disodium benzene-*o*-ditelluroate in ethanol, the latter generated *in situ* through reduction of poly(*o*-phenylene)ditelluride **55** with NaBH_4 (88KGS1144; 91MI1). The polymeric ditelluride **55**, in turn, was obtained from a two-step procedure starting with bis-(*o*-trimethylsilyl)-benzene.



The same method was employed in the syntheses of benzo-1,3-ditelluroles bearing substituents in position 2 of the five-membered ring (91UP2, 91UP3).

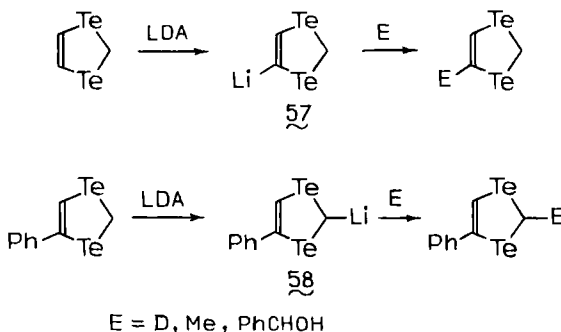


Another approach to the benzo-1,3-ditellurole **54** is founded in the reaction of bis(*o*-trimethylsilyl)benzene with the easily accessible bis(trichlorotelluro)methane (85JA675). The 1,1,3,3-tetrachlorobenzo-1,3-ditellurole **56** is reduced to **54**, yield 18–20% (91MI1).

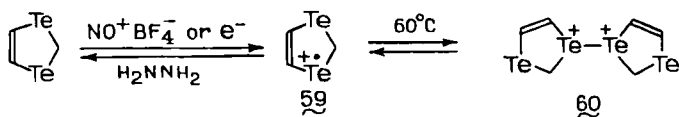


2. REACTIONS

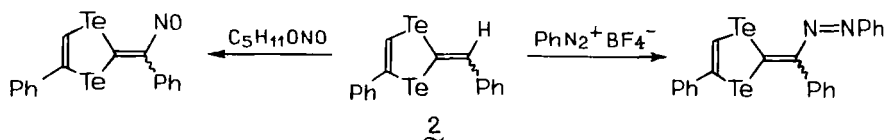
The reactivity of 1,3-ditellurole has been inadequately investigated. Lithiation of the simplest 1,3-ditelluroles with lithium diisopropylamide (LDA) leads (depending on their structure) to either 2- or 4(5)-lithio derivatives (83TL237). Thus, 4-lithio-1,3-ditellurole **57** is formed from 1,3-ditellurole, whereas lithiation of its 4-phenyl derivative produces 2-lithio-4-phenyl-1,3-ditellurole **58**. The latter result is explained by the steric hindrance that the 4-phenyl substituent creates for the attack of LDA at position 5 of the five-membered ring.



Electrochemical oxidation of 1,3-ditellurole leads to its stable radical cation **59** ($\lambda_{\max} = 560$ nm), which is also formed when nitrosonium tetrafluoroborate in CH_2Cl_2 is employed as an oxidant (85JA6298). Treatment with hydrazine hydrate smoothly restores the initial ditellurole. Similar to the radical cation of naphtho[1,8-cd][1,2]ditellurole (81CB2622), **59** does not display an ESR signal and dimerizes to dication **60** ($\lambda_{\max} = 610$ nm) on lowering the temperature of the solution to -60°C . The formation of **60** is facilitated by an increase in the concentration of the 1,3-ditellurole.



Like its sulfur and selenium analogs, 2,6-diphenyl-1,4-ditellurofulvene **2** on treatment with amyl nitrite and phenyldiazonium tetrafluoroborate undergoes electrophilic substitution at the terminal methine carbon, giving rise to the corresponding nitroso and phenylazo derivatives (81CC828).



3. Molecular Structure

Molecular and crystal structures of the parent 1,3-ditellurole were studied by use of an X-ray diffraction method (85JA6298). Figure 6 displays the molecular geometry of 1,3-ditellurole.

Attractive intermolecular Te . . . Te interactions were found to exist in a crystal as revealed by a substantial shortening of this distance (3.864 Å) compared to the sum of the tellurium Van der Waals radii.

In the ^{13}C NMR spectra of 1,3-ditelluroles **50**, signals of the C-2 nuclei display a strong high-field shift to negative δ values in the region -20.7 to -41.9 ppm (82TL1531), which is due to the shielding known as the heavy atom effect. A thorough analysis of the ^1H , ^{13}C , and ^{125}Te NMR spectra of 1,3-ditellurole enriched in ^{125}Te has been presented (86MII).

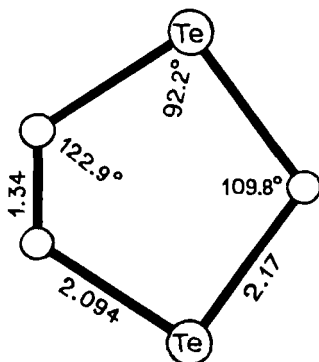
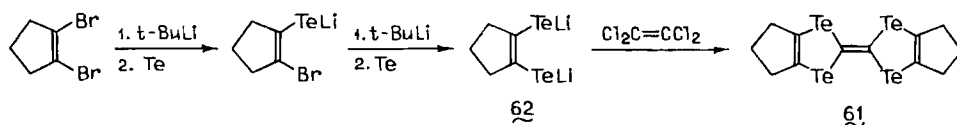


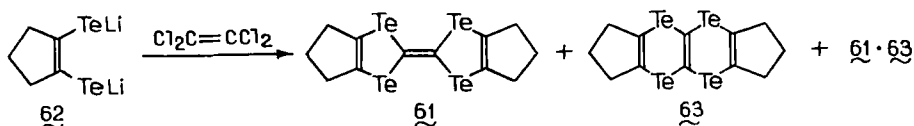
FIG. 6. Bond lengths and angles of 1,3-ditellurole molecule.

4. Tetratellurafulvalenes

a. *Synthesis.* The first known derivative of tetratellurafulvalenes (TTeF), bis(trimethylene)tetratellurafulvalene (or hexamethylenetetratellurafulvalene HMTTeF), **61** was prepared in 32% yield by coupling the dilithio salt **62** with tetrachloroethylene in THF (82JA1154). Along with HMTTeF **61**, another compound more soluble in CS₂ was isolated, its structure remaining at the time undetermined.

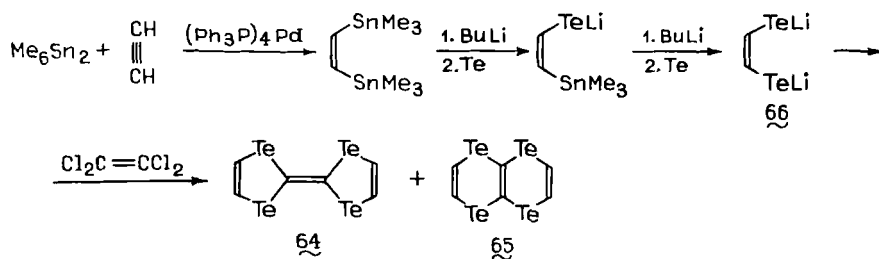


Reinvestigation of this reaction revealed that the above by-product is the isomer of HMTTeF, tetratelluradicyclopenta[b,g]naphthalene **63** whose molecule contains two fused six-membered tellurium heterocycles (86CL311; 87MI4). Apart from the isomers **61** and **63**, an adduct that they form was also isolated.

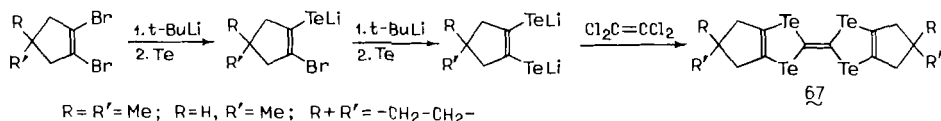


According to an X-ray crystal study (86CL311; 87MI4) of the complex **61-63**, the molecules of both its components acquire essentially a coplanar structure. The dihedral angle along the Te . . . Te line within the six-membered rings is equal to 57.1° in the complex. For the complexed and uncomplexed molecule of **61**, the analogous dihedral angles are, respectively, 14.3° and 8.2°. Another consequence of the inclusion of HMTTeF **61** into the adduct with **63** is a significant shortening of its C=C bond, 1.321 Å in complex **61-63** and 1.356 Å in the free molecule of **61** (82CC1316).

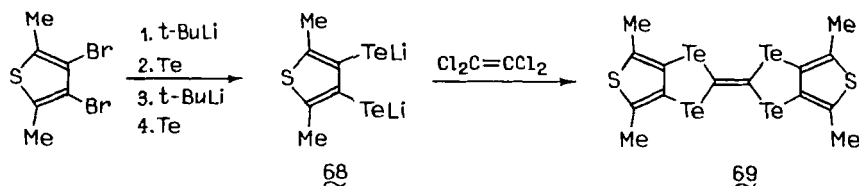
An 85 : 15 mixture of TTeF **64** and its six-membered isomer **65** is formed (total yield 36%) in the reaction of ditellurolate dianion **66** with tetrachloroethylene (87JA4115). In the same paper a new method for generation of ditellurolate dianions was suggested, 1,2-bis(trimethylstannyl)ethylene serving as a suitable precursor. The yield of TTeF may be increased if tetrabromoethylene is used in the reaction instead of tetrachloroethylene (88MI6).



The problem of the very low solubility of the majority of tellurium-containing donor component of charge-transfer complexes as well as of the radical cation salts derived from them puts certain limitations on their use and study. But the synthesis of a number of structurally modified derivatives of TTeF was accomplished. Thus, soluble derivatives of tetra-tellurafulvalenes **67** were synthesized in 20% ($\text{R} = \text{H}$, $\text{R}' = \text{Me}$) to 35% ($\text{R} = \text{R}' = \text{Me}$) yields and their structures were proved by cyclic voltametry studies (87MI6; 88MI5).

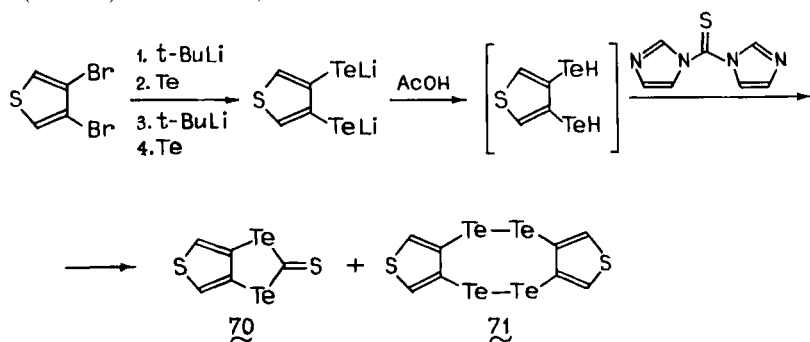


The same general methodology, the reaction of the ditelluroate dianion **68** with tetrachloroethylene, was employed for the synthesis of the thiophene-annulated TTeF. Compound **69** was obtained in 75% yield (83MI1; 84JA8303; 85MI2). No formation of the possible six-membered ring derivative was reported.

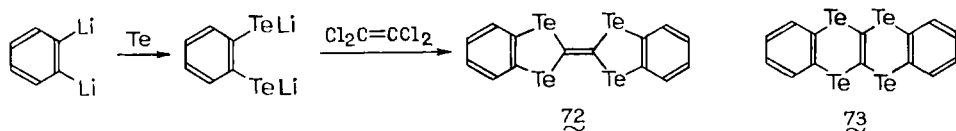


Since the "tetrachloroethylene" method of synthesis of TTeF leads, as a rule, to the formation of their isomeric six-membered by-products in the yields comparable to those of the target products, the need existed for the development of a more selective way to TTeF. The most productive is an approach based on the use as precursors of TTeF of various derivatives of 1,3-ditelluroles. A similar problem was encountered in the chemis-

try of sulfur and selenium analogs of TTeF (85AR377, 85M11; 86T1209; 87M13). A convenient way to avoid the formation of contaminating six-membered by-products was found to consist in a reductive coupling of 1,3-dichalcogenole-2-thiones (selones) under treatment with Ph_3P or $(\text{RO})_3\text{P}$. The scheme below illustrates the method of preparation of one of the useful synthons of this kind, thieno[3,4-cd][1,3]ditellurole-2-thione **70** (82M11; 83JOC4713).



Finally, the reported synthesis of dibenzotetratellurafulvalene DBTTeF **72** should be briefly commented on. This compound was prepared in a low yield of 10% by the reaction of the dilithium salt of benzene-1,2-ditellurole with tetrachloroethylene (82CC336, 82M11). Since no exhaustive spectral and structural information on the product was presented, the possibility cannot be excluded that a mixture of DBTTeF and its six-membered isomer, **73**, was formed. Therefore of current interest is the use of methods avoiding the formation of the six-membered isomers of the TTeF derivatives.



b. Electrochemical Characteristics of the Tetratellurafulvalenes and Their Analogs: Charge-Transfer Complexes and Radical Cation Salts. The oxidation potentials of the TTeF derivatives serve as the most important characteristics determining their ability to form charge-transfer complexes with different electron acceptors. Cyclic voltamperometric studies of TTeF reveal two waves, both related to reversible one-electron oxidation processes. Table III contains the oxidation potentials of the derivatives of tetratellurafulvalenes and its sulfur and selenium analogs.

TABLE III
OXIDATION POTENTIALS OF THE TTeF AND THEIR ANALOGS

Compound	$E_{1/2}$ (1), V	$E_{1/2}$ (2), V	ΔE , V	Reference
Tetrathiafulvalene	+0.47 ^a	+0.81	0.34	87JA4115
Tetraselenafulvalene	+0.62 ^a	+0.90	0.28	87JA4115
Tetratellurafulvalene 64	+0.59 ^a	+0.84	0.25	87JA4115
Tetramethyltetrathiafulvalene	+0.36 ^a	+0.84	0.48	87JA4115
	+0.35 ^a	+0.83	0.48	82CC336; 82M11
	+0.24 ^b	+0.73	0.49	82JA1154; 82M11
Tetramethyltetraselenafulvalene	+0.55 ^a	+0.94	0.39	87JA4115
	+0.54 ^a	+0.93	0.39	82CC336; 82M11
	+0.42 ^b	+0.81	0.39	82JA1154; 82M11
Hexamethylenetetraselenafulvalene	+0.56 ^a	+0.93	0.37	87JA4115
Hexamethylenetetratellurafulvalene 67	+0.40 ^a	+0.69	0.29	82JA1154; 82M11
	+0.39 ^b	+0.64	0.25	86CL311; 87M14
	+0.12 ^c	+0.34	0.22	87M16
Dimethylhexamethylenetetratellurafulvalene 67	+0.08 ^c	+0.34	0.26	88M15
Tetramethylhexamethylenetetratellurafulvalene 67	+0.10 ^c	0.31	0.21	87M16; 88M15
Di(cyclopropyl)hexamethylenetetratellurafulvalene 67	+0.11 ^c	0.34	0.23	87M16; 88M15
Bis(dimethylthieno)tetratellurafulvalene 69	+0.78 ^a	+1.20	0.42	84JA8303
	+0.40 ^c	+0.80	0.40	87M16; 88M15
Dibenzotetrathiafulvalene	+0.71 ^a	+1.14	0.43	82CC336; 82M11
Dibenzotetraselenafulvalene	+0.78 ^a	+1.17	0.39	82CC336; 82M11
Dibenzotetratellurafulvalene 72	+0.71 ^a	+1.05	0.34	82CC336; 82M11

Note. The values of $E_{1/2}$ are obtained in ^aCH₂Cl₂, ^bPhCN, ^cPrCN.

Tetratellurafulvalenes readily form charge-transfer complexes with a large number of typical electron-acceptors, TCNQ and its derivatives (F₄TCNQ, Me₂TCNQ, (MeO)₂TCNQ) and various substituted *p*-quinones among these. The most thoroughly studied charge-transfer complexes are those formed by hexamethylenetetratellurafulvalene **61** (82JA1154; 83CL503; 85M13, 85M14; 86M13). The electric conductivity of charge-transfer complexes of **61** with TCNQ and its derivatives lies, depending on the crystal structure and substituents in the electron-acceptor counterpart, in the extremely wide range of 10⁻¹⁰–7 ohm⁻¹cm⁻¹. The largest value is related to the complex of **61** with TCNQ (83CL503; 85M13). For the charge-transfer complex of the analogous tetrathiafulvalenes with TCNQ, the magnitude of the electric conductivity in a crystal equals 5.3 ohm⁻¹cm⁻¹. The complexes with TCNQ of the derivatives of TTeF, such as bis(dimethylthieno)TTeF (85M12), dimethylhexamethylene-TTeF, tetramethylhexamethylene-TTeF, and dicyclopropylhexam-

ethylene-TTeF (87MI6; 88MI5) possess very low electric conductivity in a crystal (10^{-10} – 10^{-3} ohm $^{-1}$ cm $^{-1}$). The largest magnitude is characteristic of the complex formed with TCNQ by unsubstituted TTeF (1800 ohm $^{-1}$ cm $^{-1}$) (88MI4, 88MI7). This value correlates with the respective values of analogous complexes of tetrathia (500 ohm $^{-1}$ cm $^{-1}$) and tetraselenafulvalene (800 ohm $^{-1}$ cm $^{-1}$) and clearly indicates a substantial increase in electric conductivity in the sequence S < Se < Te.

By electrochemical oxidation a series of salts of TTeF radical cations has been prepared containing different counter-ions PF $_6^-$, AsF $_6^-$, ClO $_4^-$, I $_3^-$, Cl $^-$, Br $^-$, and I $^-$ (85CL419, 85MI2; 86CL1105, 86CL1343; 87MI6). The electrical conductivity of these salts in crystal spans the interval of values between 10^{-3} and 390 ohm $^{-1}$ cm $^{-1}$.

c. *Molecular Structure.* The molecular structures of hexamethylenetetratellurafulvalene **61** (82CC1316) and bis(dimethylthieno)tetratellurafulvalene **69** (84JA8303; 85MI2) were investigated by X-ray diffraction. (Fig. 7).

Hexamethylenetetratellurafulvalene **61** possesses a symmetric chair conformation, the dihedral angles formed by bending along the Te—Te axis equal 7.7° and 8.2° (82CC1316; 85MI2). By contrast, a boat conformation and larger values of the dihedral angles (16.0° and 47.1°) are inherent in the TTeF derivative **69**. At the same time the bond distances and the valence angles in these derivatives of TTeF are close in value. It is noteworthy that as crystals both hexamethylene-TTeF **61** and bis(dimethylthieno)-TTeF **69** reveal rather strong intermolecular Te . . . Te bonds justified by their distances, 3.583 and 3.743 Å in the case of **61** and 3.666 and 3.758 Å in the case of **69**.

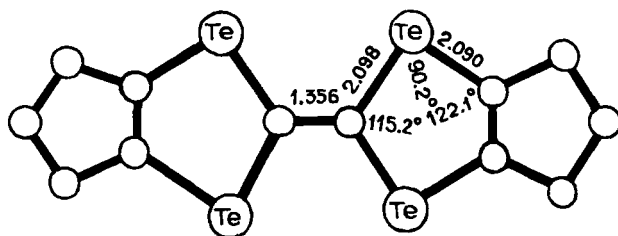
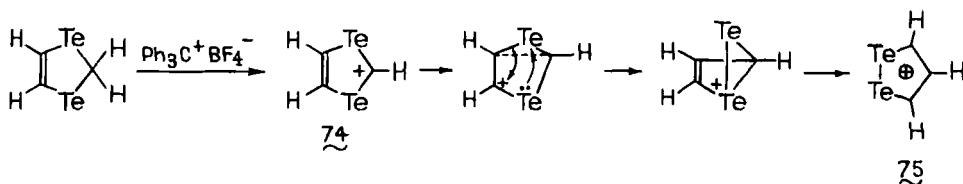


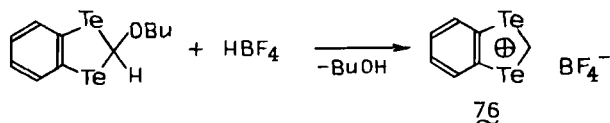
FIG. 7. Bond lengths and angles of hexamethylenetetratellurafulvalene molecule.

I. 1,3-DITELLUROYLIUM SALTS

Thus far no reports have appeared on the isolation of 1,3-ditellurolylium cation salts in a pure state. Attempts to prepare 1,3-ditellurolylium boron tetrafluoride and its derivatives via treatment of 1,3-ditelluroles with triphenylmethyl boron tetrafluoride in MeCN solution failed (82TL1531). However, formation of the 1,3-ditellurolylium cation **74** was revealed by the ^1H NMR spectrum in which the 2-H proton was shown to give a very low-field triplet (δ 15.0 ppm, $^4J_{\text{HH}} = 1.2$ Hz). Cation **74** is sufficiently stable in solution only at low temperature. When an acetonitrile solution of **74** obtained from 1,3-ditellurole was heated to 30°C , the initial ^1H NMR spectrum drastically changed to the A_2X spectral pattern (δ 13.8 ppm, d and 10.3 ppm, t , $^3J = 6.9$ Hz) corresponding to the spectrum expected for the 1,2-ditellurolylium cation **75**. A plausible reaction scheme is shown below. A further elevation of the temperature of the solution resulted in an unidentified destruction process accompanied by the extrusion of elemental tellurium.



Benzo-1,3-ditellurolylium tetrafluoroborate **76** turned out to be the first preparatively isolated salt of a heterocyclic carbocation containing two tellurium atoms in a ring (91UP3). The synthesis of **76** was carried out, similar to its sulfur analog benzo-1,3-dithiolylium boron tetrafluoride (76BCJ3567), by treatment of a solution of 2-butoxybenzo-1,3-ditellurole in acetic anhydride with 2 equivalents of HBF_4 .



IV. Six-Membered Heterocycles

We consider six-membered tellurium-containing heterocycles in the following sequence: saturated monocyclic systems (1-hetera-2(3)(4)-telluracyclohexanes), unsaturated monocyclic systems (1-hetera-4-tellura-

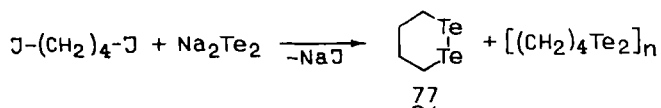
cyclohexa-2,5-dienes), and tricyclic systems (5-hetera-10-tellura-5,10-dihydroantracenes). No data on the synthesis of bicyclic tellurium-containing heterocycles with two heteroatoms have been reported yet.

A. 1-HETERA-2(3)(4)-TELLURACYCLOHEXANES

There may be five different types of 1-hetera-2(3)(4)-telluracyclohexanes, three of them relating to the group of 1,4-heterocyclic systems. Of 1,3-heterocycles, only 1,1-dimethyl-1-sila-3-telluracyclohexanes are described so far. Recently the first and only representative of 1,2-heterocyclic tellurium-containing compounds has been synthesized.

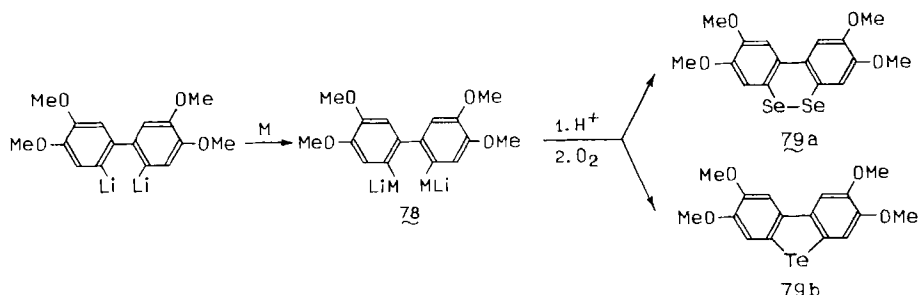
1. 1,2-Ditelluracyclohexane

1,2-Ditelluracyclohexane **77** was obtained in low yield (11%) by coupling 1,4-diiodobutane with Na_2Te_2 in DMF [88JOM(338)9]. When the phase-transfer catalysis technique was applied and the reaction was carried out in H_2O –benzene the yield of **77** was slightly increased to 15%. Along with **77**, the polymeric compound $[(\text{CH}_2)_4\text{Te}]_n$ was formed in a substantial amount.



Attempts to obtain benzo derivatives of 1,2-ditelluracyclohexane by reactions of Na_2Te_2 with either α,α -dichloro-*o*-xylene or phthaloyl chloride were unsuccessful. The reactions were accompanied by an extrusion of tellurium and resulted in the formation of the previously described 3,4-benzo-1-telluracyclopentane (75CC1893) and tellurophthalic anhydride (78OPP289), the yields of the products being, respectively, 15 and 11%.

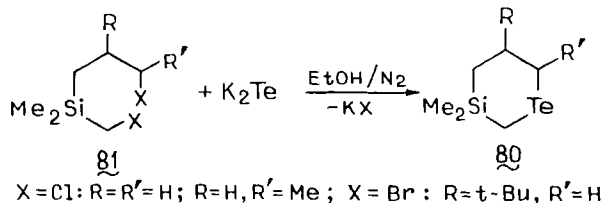
The tendency of intermediate heterocyclic ditellurides to eliminate one of the tellurium atoms thus contracting the size of the ring is illustrated by the course of the oxidative cyclization of the dilithio dichalcogenides **78** (84JHC413). Whereas in the case of the diselenolate **78** ($\text{M} = \text{Se}$) the expected heterocyclic diselenide **79a** is formed, albeit in low yield, the analogous reaction with the ditellurolate **78** ($\text{M} = \text{Te}$) results in an extrusion of elemental tellurium affording dibenzotellurophene **79b**.



2. 1,1-Dimethyl-1-sila-3-telluracyclohexane

These unstable compounds **80** were prepared in approximately 50% yield by reaction of potassium telluride with compounds **81** (76BSB319).

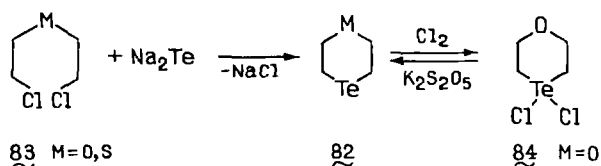
Although this cyclization is similar to those employed in the syntheses of oxygen and sulfur analogs of heterocycles **80** by reaction of **81** with potassium telluride does not allow the preparation of 2-phenyl derivatives of **80**.



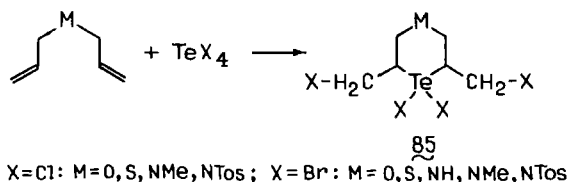
3. 1-Hetera-4-telluracyclohexanes

Methods of preparation are common for 1-oxa-4-tellura-, 1-thia-4-tellura-, and 1-aza-4-telluracyclohexanes **82**.

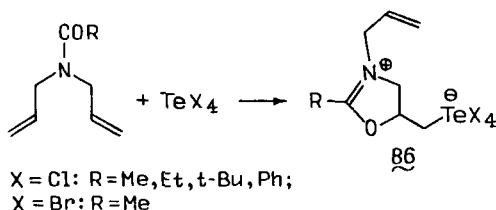
a. *Synthesis.* Three general methods for the synthesis of derivatives of 1-hetera-4-telluracyclohexanes **82** (M = O, S, NR) are known. One is based on the reaction of dihalogenides **83** with Na₂Te, the latter usually being prepared by the rongalite method. 1-Oxa-4-telluracyclohexane was isolated as 4,4-dichloro derivative **84** (M = O) in 45% yield, which smoothly reduced to **82** (M = O) by K₂S₂O₅ (45JCS11). A much lower yield (6.6%) of the final product was achieved in the case of the sulfur analog **82** (M = S) 1-oxa-4-telluracyclohexane (65IC862).



The second approach is limited to the synthesis of 4,4-dihalogeno-3,5-bis(halogenomethyl) derivatives of **82**. Compounds **85** are obtained by electrophilic addition of tellurium tetrahalogenides to diallyl oxide, sulfide, or amine under the conditions of the double phase tellurohalogenation reaction (78KGS1212; 89KGS564). The reaction follows to an anti-Markovnikov stereochemical course. The yields of the mixture of *cis*- and *trans*- isomers of compounds **85** are in the range 27–79%. By fractional crystallization the isomers of **85** (M = O, X = Br) were separated.

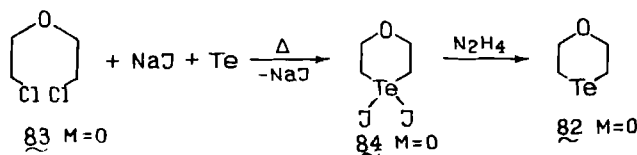


The specific chemical behavior of *N*-acyldiallylamines in their reaction with TeX_4 should be noted. In contrast to diallylamines and *N*-tosyldiallylamines, they produce the zwitterionic 2-oxazolines **86** in quantitative yields (85T1607). The structure of one of these, **86** (R = Me, X = Cl), was proved by an X-ray diffraction study.

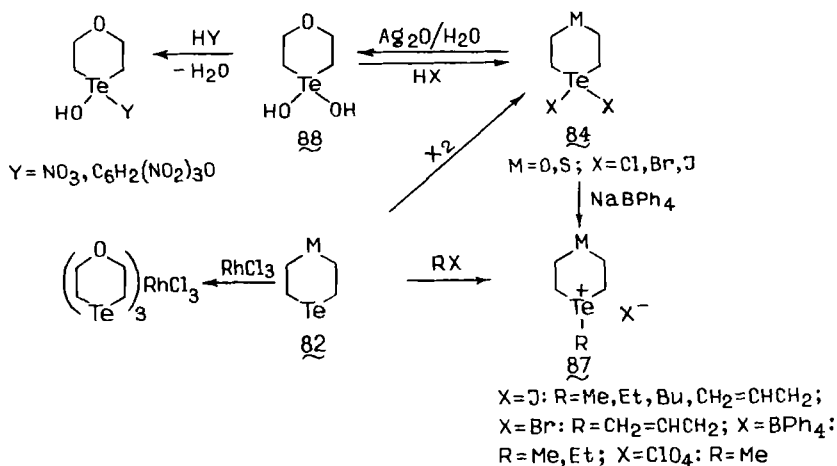


The third known method of synthesis of the heterocycles **82** is exemplified by the preparation of 4,4-diiodo-1-oxa-4-telluracyclohexane **84** on heating bis(2-iodoethyl)ether with powdered tellurium (45JCS11). It has an analogy in the synthesis of dimethyl tellurium diiodide from methyl iodide and elemental tellurium (20JCS86), but is characterized by a rather low yield (10–13%) of product **84** because of partial decomposition of the initial oxide under the reaction conditions. When bis(2-chloroethyl)ether and NaI were used instead of bis(2-iodoethyl)ether and the reaction was

carried out in 2-butoxyethanol, the yield of the compound **84** was appreciably increased (87MI2).



b. *Reactions.* Since heterocycles **82** are cyclic diorganyl tellurides, their reactivity is typical of that group of organotellurium compounds (74MI1; 83MI2). As expected 1-oxa-4-tellura- and 1-thia-4-telluracyclohexanes promptly react with halogenes forming σ -telluranes **84** through oxidative addition to tellurium centers (45JCS11; 65IC862). The tellurium salts **87** are readily formed when compounds **82** are treated with alkyl halides (45JCS11; 65IC862; 87MI2). Compounds **87** are also obtained by coupling the diiodides **84** with NaBPh_4 (87MI2); the counter-ion in telluroonium iodides (**87**, $X = \text{I}$) may be exchanged through treatment with NaBPh_4 or AgClO_4 (87MI2). As is the case of dialkyl and arylalkyl telluroxides, the heterocyclic analogs derived from **82** exist as very stable hydrates. Typical reactions of such a hydrate, viewed as a σ -tellurane with two hydroxy groups attached to the tellurium heteroatom, are illustrated in the scheme for the case of compound **88** (45JCS11). Despite the fact that diorganyl tellurides display, in general, a high donor potential to coordinate soft-acid metal compounds, the only hitherto known metal complex of **82** is that obtained from **82** ($M = \text{O}$) and RhCl_3 (90MI1).



c. *Molecular structure.* Molecular and crystal structures were determined by X-ray studies of the following derivatives of 1-hetera-4-telluracyclohexane: 4,4-diiodo-1-oxa-4-telluracyclohexane **89** (M = O, X = I) (73IC2665), its thio-analog **89** (M = S, X = I) (70IC797), and 4,4-dibromo-1-thia-4-telluracyclohexane **89** (M = S, X = Br) (72IC3026). Data on bond lengths and valency angles in the forementioned compounds are listed in Table IV. All compounds **89** examined prefer the chair molecular conformation. In a crystal, secondary intermolecular bonds between heavy atoms in σ -telluranes **89** are manifested by Te . . . I distances, 3.76 and 3.95 Å (M = S) and 3.814 and 3.692 Å (M = O), which are substantially shorter than the Te—I Van der Waals contact (4.35 Å) distances. In the case of crystalline dibromide **89** (M = S, X = Br), there are not only shortened intermolecular Te . . . Br contacts (3.591 Å, cf. the sum of the Van der Waals radii, 4.15 Å) but also similar Te . . . S contacts (3.588 Å, cf. the sum of the Van der Waals radii, 4.05 Å). In addition shortened intermolecular I . . . I contacts (3.60, 3.90 Å) are found in a crystal of 4,4-diiodo-1-thia-4-telluracyclohexane, the sum of the Van der Waals radii being equal to 4.30 Å.

Accounting for the secondary bonds considered above, the total configuration of the tellurium centers in crystalline compounds **89** ought to be octahedral or, in the case of 4,4-diiodo-1-thia-4-telluracyclohexane, as pentagonal bipyramidal, whereas nonassociated molecules **89** retain a trigonal bipyramidal configuration of bonds formed by the tetracoordinate tellurium centers.

The energy barriers (ΔG^\ddagger) to the inversion of the six-membered ring of 1-oxa-4-chalcogenacyclohexanes (chalcogen = S, Se, Te) were calculated

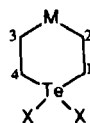


TABLE IV
BOND LENGTHS (Å) AND VALENCY ANGLES^a IN σ -TELLURANES **89**

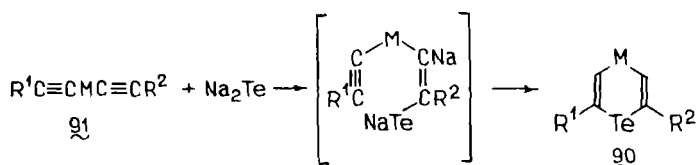
Bond lengths	X = I		X = Br	Valency angles	X = I		X = Br
	M = O	M = S			M = O	M = S	
Te—C1	2.15	2.16	2.14	C1—Te—C4	94.1	100.0	99.4
Te—C4	2.17	2.14	2.16	Te—C1—C2	112.8	115.5	117.0
Te—X	2.91	2.91	2.67	Te—C4—C3	113.5	116.0	115.0
C1—C2	1.52	1.52	1.52	X—Te—X	182.9	183.5	183.4
C2—M	1.41	1.85	1.81	C1—C2—M	113.5	113.0	114.0
M—C3	1.41	1.80	1.79	C2—M—C3	114.2	99.5	100.6
C3—C4	1.52	1.51	1.53	M—C3—C4	114.0	115.5	116.0

^a Mean values of the bond lengths and valency angles are given.

from the coalescence temperature of the AA'BB'methylene proton systems. For 1-oxa-4-thiacyclohexane and 1-oxa-4-selenacyclohexane the ΔG^\ddagger values are 46.0 and 42.6 KJ mol⁻¹, respectively [75JCS(P2)1354]. The tellurium analog shows greater stereochemical nonrigidity; its conformational rearrangement cannot be frozen even by cooling a CFC1₃ solution to 155 K, at which temperature its ¹H NMR spectrum still is represented by an averaged pattern for the methylene signal. The sequence of the energy barriers to ring inversion 1-oxa-4-chalcogenacyclohexanes O > S > Se > Te indicates an increase in conformational flexibility with lengthening the C—M bonds.

B. 1-HETERA-4-TELLURACYCLOHEXA-2,5-DIENES

A general method of synthesis of 1-hetera-4-telluracyclohexa-2,5-dienes **90** is founded in the nucleophilic addition of telluride anion to type **91** diacetylene derivatives. The telluride dianion is prepared *in situ* from the elements in liquid ammonia. The reaction was carried out with methanol or mixtures with DMSO and liquid ammonia as solvents, with the following diacetylenes: di(1-alkynyl)sulfides (73RTC1326), 1-alkynylethynyl sulfides (75RTC163), di(1-alkynyl)sulfones (78RTC244), and di(1-alkynyl)phosphinoxides (75RTC92).



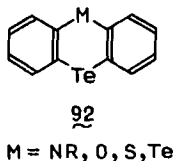
M = S: R¹ = H, R² = Me (55%), Et (54%), t-Bu (53%), CH₂=CMe (56%); R¹ = R² = H (70%), Me (78%), t-Bu (78%); M = SO₂: R¹ = R² = Me (65%), t-Bu (80%); M = P(O)Ph: R¹ = R² = H (70%), Me (71%), t-Bu (25%); M = P(O)C₆H₁₁-cyclo: R¹ = R² = H (65%), Me (58%), t-Bu (45%).

The analogous reactions with diacetylenes **91** were performed also with sodium sulfide and sodium selenide, their rates progressively increasing in the order Na₂S < Na₂Se < Na₂Te.

C. TRICYCLIC COMPOUNDS

The tricyclic tellurium-containing compounds **92** are the most thoroughly studied group of the tellurium heterocycles. Moreover, phenoxatelurine (**92**, M = O) synthesized by Drew (26JCS223) some 70 years ago

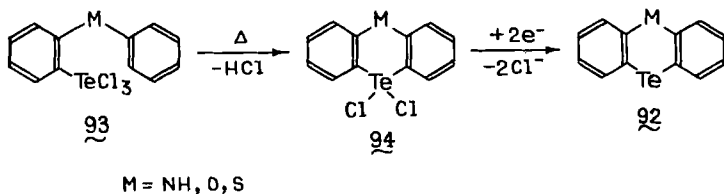
represents the first tellurium-containing heterocyclic compound with two heteroatoms. The last few years have seen considerable development in the chemistry of phenotellurazines **92** ($M = NR$) and tellurantrene ($M = Te$).



1. Synthesis

Two important methods of synthesis of heterocycles **92** ($M = NR, O, S$) are described in Sections a and b. As explained below these methods cannot be applied to the synthesis of tellurantrene **92** ($M = Te$). Therefore, the relevant approaches to **92** ($M = Te$) will be considered separately.

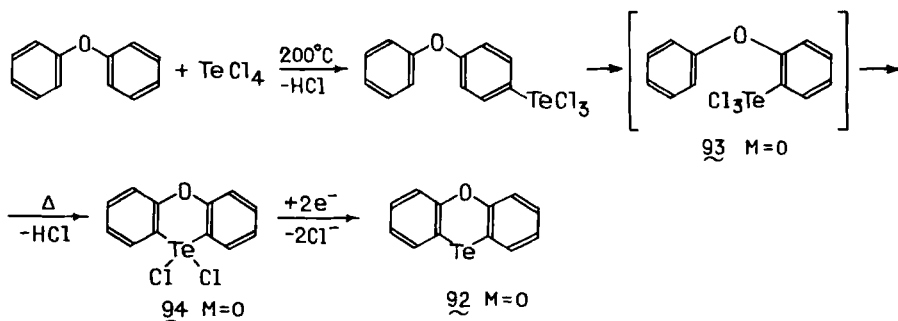
a. *Cyclizing Reactions of 2-Phenyloxy(phenylthio,phenylamino)phenyltellurium Trichlorides.* Intramolecular electrophilic cyclization of aryltellurium trichlorides **93** is the most studied method employed for the preparation of tricyclic heterocycles **92**. The cyclization leads to the Te,Te-dichlorides **94**, which may be smoothly converted to heterocycles **92** by common reducing agents, such as $K_2S_2O_5$, K_2SO_3 , $KHSO_3$, $Na_2S \cdot 9H_2O$, and N_2H_4 .



The transformation **93** \rightarrow **94** is usually conducted as a thermal reaction, conditions being determined by the nature of heteroatom M . In general, the more powerful the electron-releasing properties of the heteroatom the lower is the temperature at which the reaction proceeds. For example, the cyclization of 2-(phenylamino)phenyltellurium trichloride **93** ($M = NH$) occurs in boiling acetic acid (89H1007), whereas heating at 200°C and 240°–250°C is necessary to realize the cyclization of analogous oxide **93** ($M = O$) (26JCS223) and sulfide **93** ($M = S$) (60TI5). By using the strong Lewis acid $AlCl_3$ as a catalyst, it is possible to lower the temperature at

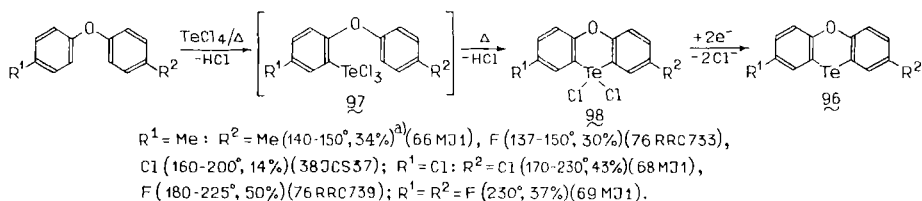
which cyclization proceeds. A plausible mechanism involves the formation of an intermediate ionic complex, $[\text{ArTeCl}_2]^+[\text{AlCl}_4]^-$, similar to that formed by interaction of AlCl_3 with TeCl_4 (71MI1). The electrophilicity of the tellurium center in this complex is markedly enhanced, facilitating its attack on the *o*-carbon of the bridged aryl ring. Indeed, when AlCl_3 was employed as a catalyst for the cyclization of 2-(benzyl)phenyltellurium trichloride, formation of 10,10-dichlorotelluroxanthene **94** ($\text{M} = \text{CH}_2$) occurred in 80% yield at 65–70°C (78KGS1567; 80KGS1342) even though the electron-releasing properties of the methylene group are less than those of oxygen and other heteroatoms in **93**.

Of special interest is the finding that 10,10-dichlorophenoxatellurine and 10,10-dichlorophenotellurazine were obtained in 50 and 7% yields, respectively from isomers of compounds **93** in which the TeCl_3 group is placed in the *p*-position relative to the oxa and amino-bridges. The reaction conditions are quite similar to those for transformations of **93**. Evidently, the *p*- TeCl_3 group migrates to the *o*-position and the resulting *o*-phenoxy-(amino) tellurium trichlorides **93** undergo cyclization to **94**. This migration is corroborated by the fact that when *p*-phenoxyphenyltellurium trichloride is heated above its melting point (156°C) it rearranges into *o*-phenoxyphenyltellurium trichloride **93** ($\text{M} = \text{O}$), which is not isolated analytically pure. Hence, the most convenient method of obtaining 10,10-dichlorophenoxatellurine **94** ($\text{M} = \text{O}$) is by heating equimolar amounts of tellurium tetrachloride and diphenyl oxide without isolation of intermediate **93** ($\text{M} = \text{O}$) [26JCS223; 75CS(A)116].

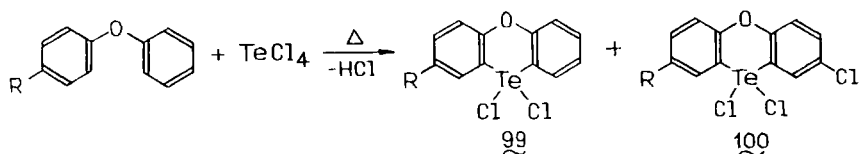


Information on the preparation of the 10,10-dichlorophenothiatellurine **92** ($\text{M} = \text{S}$) by use of a similar method is contradictory. According to the data (60T15), the reaction of TeCl_4 with diphenyl sulfide does not lead to **92** ($\text{M} = \text{S}$), but stops at the stage of 4-(phenylthio)phenyltellurium trichloride. On the other hand, it was reported (70RRC1967) that heating TeCl_4 with an excessive amount of diphenyl sulfide at 190–200°C for

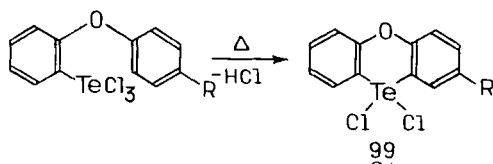
However, a number of other diaryl oxides, 4-chloro-4'-bromo-, 4-chloro-4'-nitro- (76RRC733), 4,4'-dibromo- (73MI1), 4-bromo-, 4-iodo- (76RRC739), and 4-nitro- (27JCS116), on reacting with TeCl_4 do not afford phenoxatel-



lurines. The method above is, however, of limited use when applied to the synthesis of 2(8)-substituted 10,10-dichlorophenoxatellurines **99** since, along with these, considerable amounts of 2-*R*-8,10,10-trichlorophenoxatellurines **100** are formed owing to the introduction of chlorine into the unsubstituted *p*-position of one of the aromatic ring. Thus, upon heating of 4-methyl- (27JCS116; 28JCS506), 4-fluoro-, and 4-chlorodiphenyl oxides (76RRC739) with TeCl_4 at elevated temperature difficultly separable mixtures of compounds **99** and **100** are obtained, the latter being formed due to partial decomposition of tellurium tetrachloride into tellurium and chlorine and subsequent chlorination of **99** catalyzed by TeCl_4 (58MII; 59USP2938059).



A more general method of preparation of various 10,10-dichlorophenoxatellurines comprises intramolecular electrophilic cyclization of 2-phenoxyphenyl tellurium trichlorides, which are readily accessible from the corresponding arylmercury chlorides or aryltrimethylsilanes (83M12).

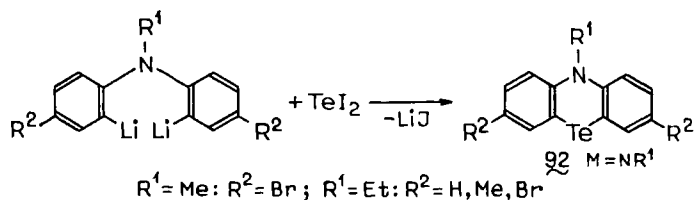


The principal advantage of this method over those above is that electron-withdrawing groups *R* in the precursor do not inhibit the cyclization reaction to give 10,10-dichlorophenoxatellurines **99**. This reaction is useful for the preparation of phenoxatellurines containing substituents in the TeCl_3 -substituted ring or in the *p*-position (with respect to oxygen) of another ring. If, however, the substituents in the second ring are in

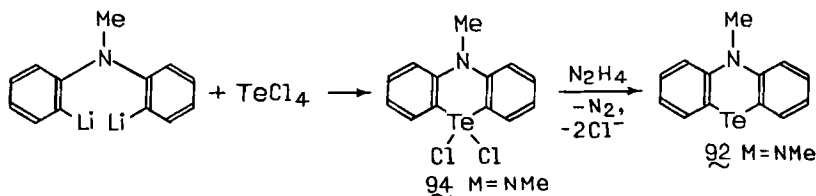
o- or *m*-positions, then the formation of a mixture of isomeric 10,10-dichlorophenoxatellurines is expected.

The cyclization of 2-(phenoxy)- and 2-(phenylthio)phenyltellurium trichlorides so useful in the synthesis of phenoxa- and phenothiatellurines cannot be applied to the preparation of tellurantrene **92** (M—Te). The interaction of diaryl tellurides with tellurium tetrachloride leads to the formation of diaryltellurium dichloride in which a very strong electron-withdrawing TeCl₂ group (77ZOB2541) inactivates the aryl rings to a further electrophilic attack by a second molecule of TeCl₄.

b. *Preparation from 2,2'-Dilithiodiarylamines*. A number of phenotellurazines **92** (M = NR) have been synthesized in yields of 45–55% by reaction of 2,2'-dilithio-*N*-alkyldiaryl amines with TeI₂ [82IDOK-(266)1164; 82KGS707; 85KGS757; 88MI1] or TeCl₄ [83JOM(251)223]. Although no limitations are expected when the method is extended to the synthesis of other tricyclic heterocycles **92** (M = O, S, Se, Te), no reports on their preparation from respective 2,2'-dilithiodiaryl oxides, sulfides, and tellurides have yet appeared in the literature.

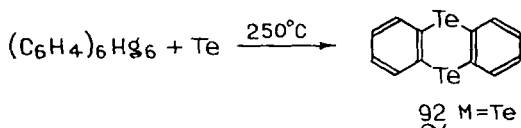


When TeCl₄, instead of TeI₂, is employed in a reaction with *o,o'*-dilithio derivatives of diarylamines, the yields of phenotellurazines are three times lower and the additional step of reduction of the dichloride **94** (M = NR) must be included.

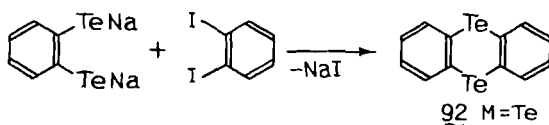


c. *Tellurantrene*. The first report on the synthesis of tellurantrene **92** (M = Te) by reaction of tetraphenyl tin with tellurium appeared in 1964 [64ZN(B)74], but subsequent attempts to reproduce it failed [80JFC245;

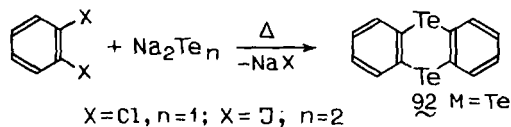
81JOM(212)141] and the properties of well-characterized tellurantrene differ from those described in the first communication on its preparation. The first unambiguous synthesis of tellurantrene in over 70% yield was realized upon heating relatively inaccessible hexameric *o*-phenylenemercury with powdered tellurium [81JOM(212)141].



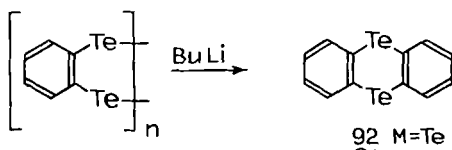
A number of methods developed for the preparation of tellurantrene are based on reactions stipulated by the high nucleophilicity of tellurolate and telluride anions. One such method allowing the preparation of tellurantrene in 50–60% yield employs coupling benzene-1,2-ditellurolate (see Section III,H,I) with 1,2-diiodobenzene (90KGS137; 91KGS1203).



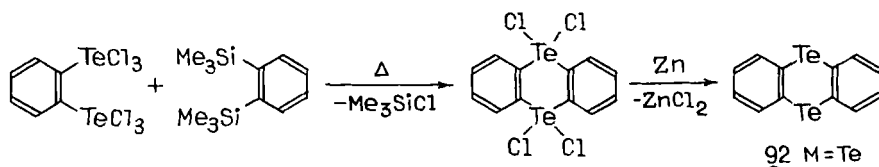
Telluranthrene was obtained in trace amounts (3%) by the reaction of *o*-dichlorobenzene with sodium telluride (88MI3) and in somewhat higher yield (12%) by the reaction of *o*-diiodobenzene with sodium ditelluride (91KGS1203). It is worth nothing that the analogous reaction of *o*-dibromobenzene with sodium diselenide leads not to selenanthrene but to poly(*o*-phenylene)diselenide in 26% yield (87IC1664).



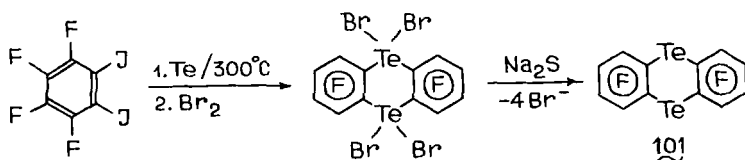
Recently a novel approach to the synthesis of tellurantrene has been suggested (91KGS1203): this employs a reaction between poly(*o*-phenylene)ditelluride and butyllithium. The assumed mechanism of formation of tellurantrene **92** (M = Te) is founded on the known ability of the Te—C (87AG1221) and Te—Te (63CB247) bonds to cleave under the action of organolithium compounds. One of the products of this cleavage, *o*-dilithiobenzene, reacts with poly(*o*-phenylene)ditelluride affording tellurantrene in approximately 30% yield.



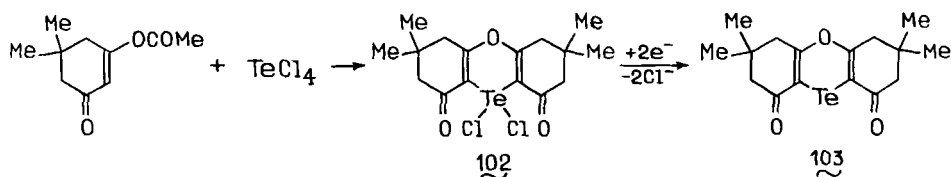
Poly(*o*-phenylene)ditelluride on oxidation by chlorine serves as a source of another precursor of tellurantrene, 1,2-bis(trichlorotelluro)benzene (91KGS1203).



The only known substituted tellurantrene is perfluorotellurantrene **101**. Its adduct with two molecules of bromine, 5,5',10,10'-tetrabromoperfluorotellurantrene, was isolated in 29% yield when *o*-diiodotetrafluorobenzene was allowed to react with elemental tellurium and then bromine was added to the reaction mixture (80JFC245). A subsequent reduction with sodium sulfide affords **101** in rather low 20% yield, unusual for the typically smooth reduction of σ -telluranes.



d. *Miscellaneous.* A derivative of phenoxatellurine **92** ($M = \text{O}$), 1,2,3,4,5,6,7,8-octahydro-3,3,7,7-tetramethyl-1,9-dioxo-10,10-dichlorophenoxatellurine **102** was obtained in 60% yield by reaction of the enol acetate of dimedone with TeCl_4 (85KGS769). Subsequent reduction of **102** leads to **103** in almost quantitative yield.

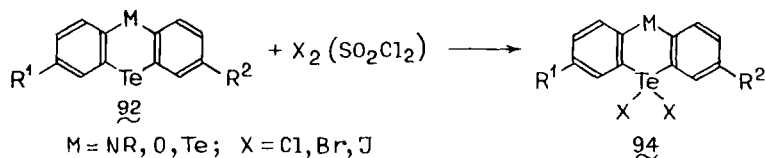


Whereas various reactions of phenotellurazines and particularly of phenoxatellurine have been thoroughly studied, information on the reactivity of tellurantrene is rather scarce and reactions of phenothiatellurine are practically unstudied. The chemical behavior of heterocyclic compounds **92** is determined by the presence in these tricyclic systems of two reaction centers represented by a tellurium and a second heteroatom M (NR, O, S) and also by a tendency of the activated benzene rings to enter into electrophilic substitution reactions. We shall follow this classification of reactions of tricyclic systems **92**.

2. Reactions at the Tellurium Center

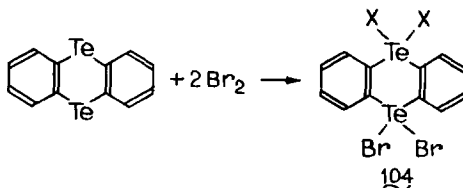
A two-coordinated tellurium center in **92** is susceptible to numerous transformations typical of those in diorganyl tellurides.

a. *Derivatives of Tetracoordinated Tellurium.* The most characteristic feature of organic compounds containing dicoordinated tellurium atoms is their inclination to undergo various oxidative addition reactions involving tellurium and transforming it to a four-coordinated state, i.e., formation of σ -telluranes. Phenotellurazines 82DOK(266)1164; 82KGS707; 85KGS757; 88M11; 89H1007), phenoxatellurines (26JCS223; 28JCS506; 66M11; 68M11; 69M11; 70RRC501; 73M11; 76RRC733, 76RRC739), and tellurantrene (91KGS1203) under very mild conditions (at ambient and lower temperature) may be oxidized to σ -telluranes **94** by chlorine, sulfuryl chloride, bromine, and iodine. As usual, almost quantitative yields of **94** were achieved. Copper(II) halogenides may also be used as oxidative addition reagents converting phenotellurazines to their 10,10-dihalogeno derivatives, but at higher temperature (85KGS757). Since 10,10-dihalogenophenotellurazines as well as other σ -telluranes of type **94** are readily produced to initial heterocycles **92**, the **92** \rightarrow **94** reaction is sometimes employed for the isolation and purification of compounds **92**.



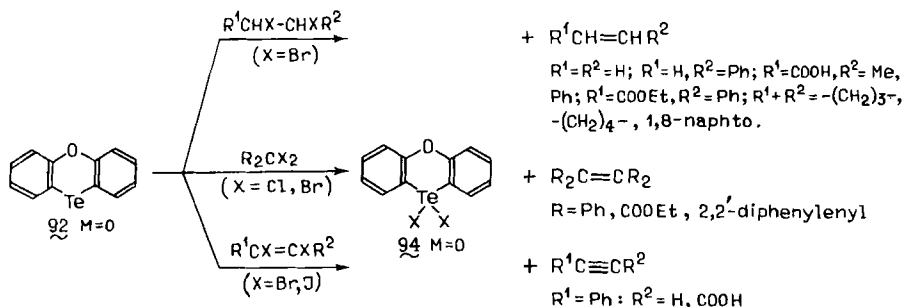
Oxidative addition of halogens to tellurantrene **92** (M = Te) apparently may result in the formation of both dihalogeno-**94** (M = Te) and tetrahalogeno derivatives **104**. The former compounds are formed upon addition of bromine and iodine to a chloroform solution of tellurantrene at room

temperature. When two equivalents of the halogene are used and the reaction is carried out in boiling chloroform, the product is 5,5,10,10-tetrahalogenotellurantrene **104** (91KGS1203).



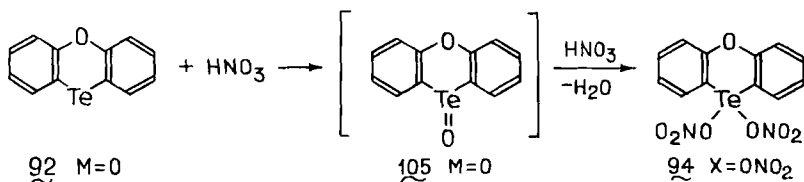
For the σ -telluranes **94**, one characteristic is the smooth exchange reaction at the tellurium center. 10,10-Dibromo(diiodo)phenoxatellurines convert to dichlorides when treated with chlorine or suluryl chloride; 10,10-diiodo derivatives under the action of bromine readily afford 10,10-dibromides and 10,10-dichloro- and 10,10-dibromophenoxatellurines are easily transformed to 10,10-diiodo derivatives when potassium iodide is added to their methanolic solutions (70MI2).

The ease with which phenoxatellurine and its analogs **92** form heterocyclic σ -telluranes **94** allows them to be used in preparative applications (mostly phenoxatellurine). They serve as useful reagents for the dehalogenation of vicinal (70MI1) and geminal dihalides (70RRC1967) to produce alkenes and alkynes in rather high yield [see Campos and Petragnani (60TL5) about the general use of diaryl tellurides for this purpose]. The dehalogenation reactions are usually carried out in refluxing toluene or xylene with equimolar amounts of the reagents. In some cases organic dihalide itself serves as the solvent. The special feature of these reactions is their high stereospecificity; the main products are E-isomers. However, their use is not completely general. Thus benzyldene chloride, benzyldene bromide, and 1,2-diphenyl-1,2-dibromoethane do not react with phenoxatellurine at all.



Diaryl tellurides promote the dehalogenation of vicinal dibromides under phase-transfer catalysis conditions (85BCJ1335). Only about 5% by weight of diaryl telluride is needed to produce alkenes in high yield in the presence of the reducing agent $K_2S_2O_5$ that restores the diaryl tellurium dibromide intermediate to the initial telluride. Further investigation of the dehalogenating ability of phenoxatellurine which is known to surpass that of diaryl tellurides and phenothiatellurine (70RRC1967) would be of significant preparative interest.

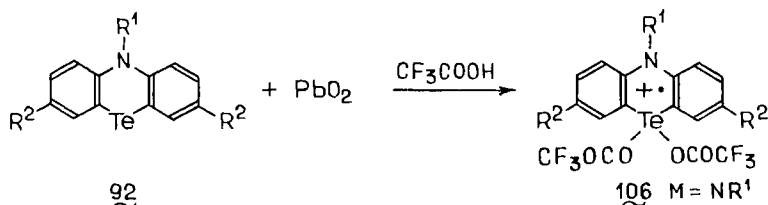
Phenoxatellurine **92** ($M = O$) and its derivatives can be easily oxidized with dilute nitric acid to the corresponding 10,10-dinitrates in high yield (26JCS223, 26JCS3054). When concentrated nitric acid is employed the reaction does not stop at the 10,10-dinitrate **94** ($X = ONO_2$) stage, but leads to further nitration of the benzene ring (27JCS116). This is also the case of the nitration of phenotellurazine (85KGS757). The most plausible mechanism of formation of type **94** ($X = ONO_2$) compounds includes the intermediacy of telluroxide **105** emerging through oxidation of **92** by nitric acid. With excess HNO_3 the teluroxide **105** gives rise to dinitrate **94** ($X = ONO_2$).



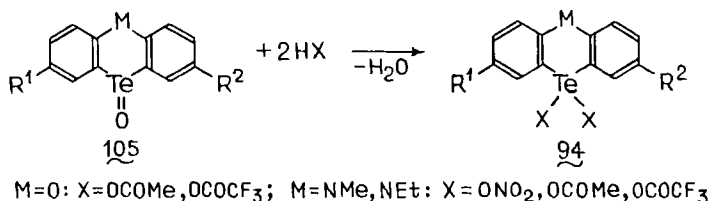
A bluish-violet coloration of the solution of phenoxatellurine upon addition of dilute nitric acid to it is observed; this precedes the formation of colorless 10,10-dinitrate **94** ($X = ONO_2$) (26JCS3054). The same color is characteristic of solutions of **94** ($X = ONO_2$) to which such a strong reducing agent as H_2SO_3 is added and also of powders obtained by rubbing a mixture of crystalline compounds **92** ($M = O$) and **94** ($M = O$, $X = ONO_2$). Similarly, when phenoxatellurine is dissolved in concentrated H_2SO_4 , the solution rapidly acquires a red color and eliminated SO_2 , manifesting the formation of 10,10-dihydrosulfate **94** ($X = OSO_3H$), preparatively isolated in a form of their complexes with H_2SO_4 and H_2O . The colored intermediates were assigned as radical cation salts in the course of oxidation of phenoxatellurine and phenotellurazine. This explanation is corroborated by the results of electrochemical oxidation of phenoxatellurine (POT) in acetonitrile containing $LiClO_4$ (66BSF2510; 73BSF2870). The radical cation intermediate rapidly transforms to a dimer

($\lambda_{\max} = 525$ nm) that adds a molecule of POT giving rise to the preparatively isolated complex $[\text{POT}(\text{POT}^+)_2](\text{ClO}_4^-)_2$ ($\lambda_{\max} = 425$ nm).

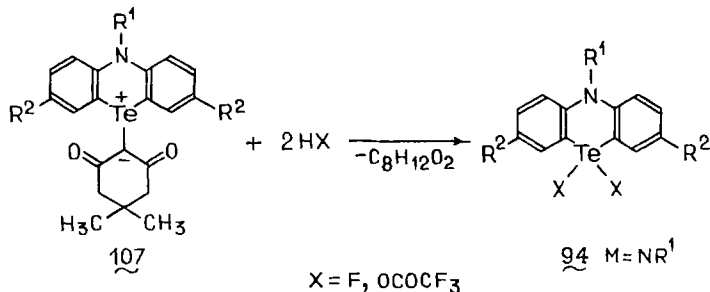
Stable radical cations **106** were also generated by oxidation of *N*-alkylphenotellurazines by PbO_2 in trifluoroacetic acid (85KGS757). Well-resolved ESR spectra of **106** show a significant delocalization of the unpaired electron over the conjugated system.



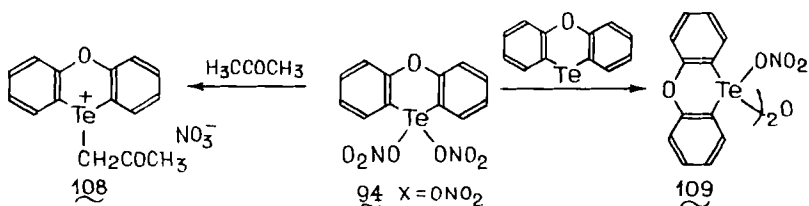
Reaction of phenoxatellurine with hydrogen peroxide (26JCS3054; 34JCS1790) or NaNO_2 (26JCS3054) in acetic acid leads to the formation of telluroxides **105**, which on being treated with various carbonic acids afford σ -telluranes **94**. No preparative isolation of **105** is needed. When trifluoroacetic acid is employed in this reaction the role of oxidant may be played by the air (73CSC629); however, the actual mechanism of the reaction is probably more complicated.



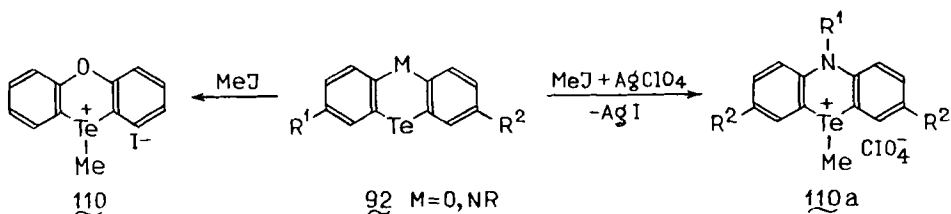
σ -Telluranes, derivatives of phenotellurazine were also obtained by the reaction of protonic acids with ylides **107** (85KGS757).



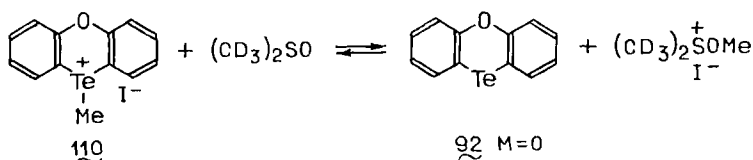
Two interesting reactions of phenoxatellurine 10,10-dinitrates, unknown for the dinitrates derived from acyclic diaryl tellurides, were discovered. On reacting with acetone, compound **94** ($M = O$, $X = \text{ONO}_2$) unexpectedly produces acetonyl phenoxatelluronium nitrate **108** (73JHC537), whereas mixing **94** ($M = O$, $X = \text{ONO}_2$) with phenoxatellurine affords compound **109** (73JHC543). The structure of compounds **108** and **109** was proved by X-ray analyses.



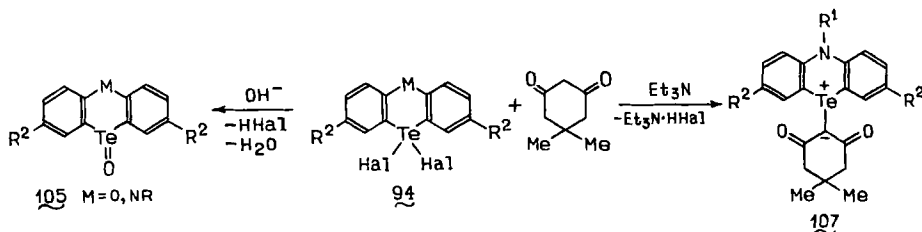
b. *Derivatives of Tricoordinated Tellurium.* The high nucleophilicity of the dicoordinated tellurium center in compounds **92** provides for the ready formation of type **110** telluronium salts through reaction of **92** with common alkylating agents. In the case of phenoxatellurine **93** ($M = O$), a reaction with methyl iodide occurs upon heating reagents in a sealed ampule (84MI1). Methylation of phenotellurazines **92** ($M = \text{NR}$) ought to be promoted by the addition of AgClO_4 (85KGS757).



Telluronium salts like **110** are themselves very strong alkylating agents, which is illustrated by the equilibrium observed in $\text{DMSO}-d_6$ solution (84MI1).



To tricoordinated tellurium-containing compounds belong also π -telluranes, telluronium ylides, imides, and oxides. Heterocyclic telluroxides **105** were obtained in analytically pure form from dihalides **94** treated with Ag_2O (34JCS1790) or NaOH (85KGS757). By coupling dihalides with dimedone in the presence of stoichiometric amounts of Et_3N , ylides **107** were prepared (85KGS757).



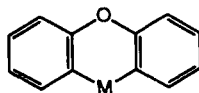
c. *Complexation Reactions.* Derivatives of dicoordinated tellurium, including tricyclic compounds **92**, should be considered to be soft organic bases. In accordance with the HSAB principle (85T1) these are prone to interact with soft Lewis acids. It was found that phenoxatellurine and *N*-alkylphenotellurazines readily form complexes with various salts (85KGS757) and carbonyls of typical soft metals, manganese (62CB2027), and rhodium [82DOK(266)1164; 84MI2].

Heterocycles **92** also exhibit marked electron-donating properties, reacting with different organic acceptors (1,3,5-trinitrobenzene (TNB) (69BAP1, 69BAP333; 70RC1713), 1-hydroxy-2,4,6-trinitrobenzene (PA) (69BAP1), 1-chloro-2,4,6-trinitrobenzene (PC) (69BAP1), tetracyanoethylene (TCNE) (70RRC309; 74CJC3814), and TCNQ [80CJC1133; 84JCS(D)1267] to form stable 1:1 charge-transfer complexes, some of them forming good crystals.

Data on absorption maxima of the charge-transfer electronic transitions, equilibrium constants, and thermodynamic parameters for molecular complexes of phenoxachalcogenines with various acceptors are given in Table V.

Contradictory suggestions exist concerning the assignment of the structures of these complexes to the n - or π -type. The main conclusion (69BAP333; 70RC1713) is that in the case of compounds **111** ($\text{M} = \text{S}, \text{Se}, \text{Te}$), heteroatom M with its low-energy lone-pair MO serves as the donor center in forming charge-transfer complexes with trinitrobenzene and other electron-accepting compounds (n -complexes). By contrast, in the case of dibenzo-*p*-dioxine **111** ($\text{M} = \text{O}$), the filled delocalized π -orbitals of the heterocyclic system donate electrons to π^* -orbitals of the acceptor component of charge-transfer complexes. This conclusion that

TABLE V
THERMODYNAMIC PARAMETERS FOR THE FORMATION OF CHARGE-TRANSFER COMPLEXES OF PHENOXACHALCOGENINES **111** WITH ACCEPTORS



M	Acceptor	λ_{\max} (nm)	$K_{(20^\circ)}$ (l/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔS (eu)	I_D (eV)	Reference
O	TNB	410–415	12.2 ± 0.3	—	—	—	—	69BAP333; 70RC1713
	TCNE	640–650	1.6 ± 0.5	-1.95 ± 0.2	-0.00 ± 0.02	-6.7 ± 0.7	7.79^a	74CJC3814
S	TCNQ	650–670	5.29	-3.12	—	-7.35	—	80CJC1133
	TNB	420	12.8 ± 1.5	-3.2 ± 1.3	—	—	—	69BAP333; 70RC1713
	TCNE	670–680	2.0 ± 0.5	-2.1 ± 0.3	-0.04 ± 0.02	-7.2 ± 1.0	7.79^a	74CJC3814
	TCNQ	695–715	3.75	-2.41	—	-5.58	—	80CJC1133
Se	TNB	415–420	11.2 ± 1.7	—	—	—	—	69BAP333; 70RC1713
	TCNE	660–680	1.5 ± 0.5	-2.1 ± 0.2	-0.02 ± 0.02	-7.2 ± 0.7	7.71	74CJC3814
	TCNQ	670–690	6.02	-1.36	—	-1.02	—	80CJC1133
Te	TNB	440	13.2 ± 2.0	-1.9 ± 0.8	-1.52 ± 0.09	—	—	69BAP1; 69BAP333; 70RC1713
	PA	420	8.4 ± 1.8	-1.9 ± 0.8	-1.52 ± 0.09	—	—	69BAP1; 69BAP333; 70RC1713
	PC	420	8.0 ± 2.1	—	—	—	—	69BAP1
	TCNE	707 ± 3	—	—	—	—	7.60^b	70RRC309
	TCNE	700–720	1.0 ± 0.3	-2.0 ± 0.04	-0.00 ± 0.02	-6.8 ± 1.3	7.59	74CJC3814
	TCNQ	735–775	11.8	-4.93	—	-3.49	—	80CJC1133

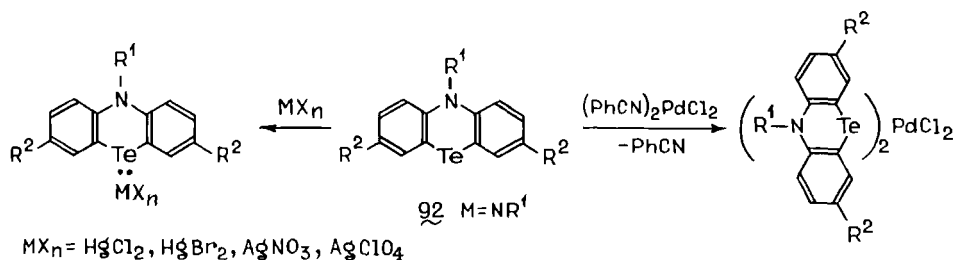
^a Donor ionization potentials were calculated with aid of the equation $0.87I_D = h\nu + 4.86$.

^b The ionization potentials of 2,8-dimethyl-, 2,8-dichloro- and 2,8-difluorophenoxatellurines are 7.54, 7.74, and 7.81 eV, resp. (70RRC309).

charge-transfer complexes formed by heterocycles **111** ($M = S, Se, Te$) are of the n -type is inconsistent with the lack of a correlation between the electronegativity of the heteroatoms M and the stability of the complexes. However, the following facts (69BAP1, 69BAP333) favor the above conclusions regarding the n - π -type of the complexes considered: (a) dimethyl telluride as well as phenoxatellurine forms complexes with trinitrobenzene; (b) trinitrobenzene complexes with diethyl sulfide and phenoxathiine have very similar UV-absorption spectra; (c) the same is true for the trinitrobenzene complexes of diphenyl oxide and dibenzo- p -dioxine.

Phenoxatellurines display a tendency to self-complexation that demonstrates their ambient character as both strong n -donors and π -acceptors. The 1:1 adduct of phenoxatellurine with 2-methyl-8-chlorophenoxatellurine (27JCS116; 28JCS506) and 2:1 adduct of 2,8-dinitrophenoxatellurine with 2-nitrophenoxatellurine (27JCS116) have been described.

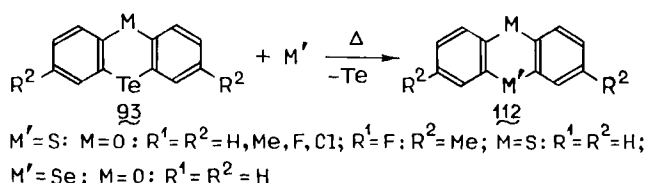
Phenotellurazine, like diorganyl tellurides (82CCR133) and telluroxanthene (80KGS1342), form molecular complexes with various soft Lewis acids, such as mercury, silver, and palladium salts (85KGS757). With mercury and silver salts, N -alkylphenotellurazines give 1:1 adducts, whereas with $PdCl_2$ two tellurium-containing ligands are involved.



On reacting with $Mn(CO)_5Cl$, phenoxatellurine forms the complex $[(POT)_2Mn(CO)_3]Cl$ (62CB2027), and N -ethyl-2,8-dimethylphenotellurazine (PTA) reacts with $[Rh(CO)_2Cl]_2$ and $PhOxq(C_8H_{14})CO$, giving rise to the corresponding $Rh(PTA)_2COCl$ and $RhOxq(PTA)CO$ [82DOK(266)1164; 84MI2]. Ligand exchange substitution reaction of phenotellurazine readily occurs when these complexes are treated with phosphines (84MI2).

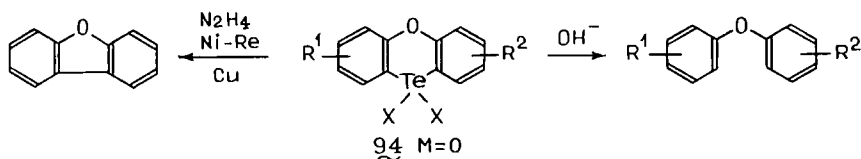
d. *Replacement of the Tellurium by Other Chalcogenes.* An important characteristic of heterocycles **92**, as well as of the majority of other tellurium-containing heterocyclic systems, is the propensity to substitute the tellurium heteroatom in a ring by sulfur or selenium on heating with elemental chalcogenes at elevated temperatures. A frequently studied

case is the exchange reaction with sulfur, but not yet for telluranthrene. Phenoxathiines, thianthrene, and *N*-alkylphenotellurazines were obtained in 44–90% yields, respectively, from phenoxatellurines (28JCS511; 66M11; 68M11; 69M11; 76RRC733, 76RRC739), phenothiatellurine (70RRC1967), and *N*-alkylphenotellurazines (85KGS757). The mechanism of the exchange reactions has not been studied in detail.



The only known example of the tellurium by selenium exchange reaction in heterocycles **92** is a conversion of phenoxatellurine **92** ($\text{M} = \text{O}$) to phenoxaselenine **112** ($\text{M} = \text{O}$, $\text{M}' = \text{Se}$) (28JCS511). A mixture of the product and unreacted **92** ($\text{M} = \text{O}$) cannot be separated by crystallization. To isolate pure phenoxaselenine, the reaction mixture was allowed to react with bromine and the resultant 10,10-dibromophenoxatellurine and 10,10-dibromophenoxaselenine were treated with acetone. Whereas the former compound is inert, the latter undergoes facile debromination, which thereby makes possible the separation of the highly acetone-soluble phenoxaselenine. Precisely this sequence of reactions was used in the first synthesis of phenoxaselenine.

e. *Extrusion of the Tellurium Atom.* On heating phenoxatellurines or their 10,10-dichloro- and 10,10-dinitrate derivatives in water containing K_2CO_3 (27JCS116) or KOH (73M11) diaryl oxides are formed in high yields. These transformations were used for the structural identification of the products of electrophilic substitution reactions (nitration, bromination) of phenoxatellurine.

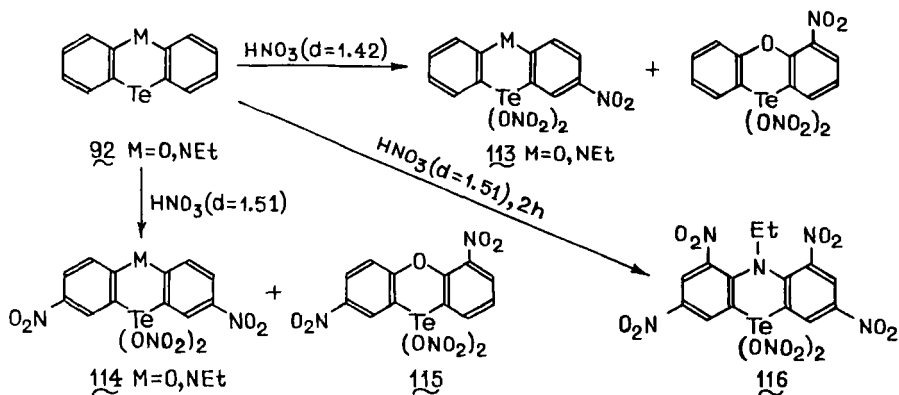


On the other hand, treatment of phenoxatellurine with degassed Raney nickel gives rise to benzofuran [75CS(A)116]. In the same way biaryls were formed from diaryl tellurides and diaryltellurium dichlorides (72T3323).

3. Electrophilic Substitution Reactions

So far electrophilic nitration and halogenation were studied only for derivatives of phenoxatellurine and *N*-alkylphenotellurazine **92** ($M = O$, NEt). The strong oxidizing agents nitric acid and halogens first convert compounds **92** to Te, Te-dinitrates or dihalogenides, which then undergo electrophilic substitution at the arene rings. The strong electron-withdrawing properties of the TeX_2 group direct *meta* and the electron-donating oxygen and nitrogen atoms direct *para* thereby reinforcing each other and regiospecifically orienting electrophiles to the 2(8) and 4(6)-positions in heterocycles **92**.

Treatment of phenoxatellurine with concentrated nitric acid ($d = 1.42$) gives, mainly, 2-nitrophenoxatellurine 10,10-dinitrate **113** ($M = O$) along with a small amount of the 4-nitro isomer (27JCS116). In the case of *N*-ethylphenotellurazine the only product isolated was 2-nitro-*N*-ethylphenotellurazine 10,10-dinitrate **113** ($M = NEt$) (85KGS757). When heterocycles **92** interacted with fuming ($d = 1.51$) nitric acid, the major reaction products were dinitro derivatives **114**. Phenoxatellurine also affords under these conditions a small amount of 4,8-dinitro derivative **115**: even on prolonged heating the third nitro group may not be introduced into phenoxatellurine. However, *N*-ethylphenotellurazine containing a stronger electron-donating alkylamino group in the ring, when treated for 2 h with fuming nitric acid gives tetra nitro product **116** having nitro groups *ortho* and *para* to the ethylamino group.



Electrochemical reduction of 2,8-dinitro- and 2-nitrophenoxatellurines in DMSO produces the corresponding radical anions [77JCS(P2)529]. In the former case, a presence of two interconverting asymmetric conformers in solution was detected by ESR. When 2-nitrophenoxatellurine was re-

duced by potassium in DMF, the ESR spectrum shows the formation of two radicals derived from 2-nitrophenoxatellurine and 4-nitrodiphenyl oxide. The formation of the latter is, apparently, a consequence of a parallel detelluration of phenoxatellurine promoted by potassium hydroxide produced by the interaction of potassium with trace amounts of water in the solvent.

Chlorination and bromination of heterocycles **92** ($M = O$), **NEt** also are directed to the 2,8-positions of phenoxatellurine (70MI2; 73MI1) and phenotellurazine derivatives (85KGS757). Addition of catalytic amounts of iodine facilitates bromination of 10,10-dihalogenophenoxatellurines and enhances the yield of the reaction. When the reaction time is sufficiently short, it is possible to isolate also a monosubstituted product, 2-bromophenoxatellurine (after reduction of the initially formed 10,10-dihalogeno derivatives) (73MI1). If 10,10-diiodophenoxatellurine (**94**, $M = O$, $X = I$) is introduced into the reaction, iodine at the tellurium center is displaced by bromine and then fulfills its function as a catalyst. Similarly, 2,8,10,10-tetrachlorophenoxatellurine was prepared in 90% yield by chlorination of **94** ($M = O$, $X = I$) (70MI2). Bromination of *N*-ethyl-phenotellurazine in the presence of iodine gave 2,8,10,10-tetrabromo-*N*-ethylphenotellurazine in 70% yield (85KGS757).

4. Reactions of Functional Groups

Various functional groups attached to the benzene rings in **92** and **94** are susceptible to their usual reactions. Thus, a 2-methyl group in 2-methylphenoxatellurine may be oxidized to a carboxylic function by potassium permanganate in neutral or alkaline water or by chromic acid; both lead to 2-carboxyphenoxatellurine in low yield. On boiling quinoline solution with copper powder, this compound evolves CO_2 and is converted into the unsubstituted phenoxatellurine **92** ($M = O$) (38JCS37). Mono- and dinitrophenoxatellurines are reduced, respectively, to mono- and diamines by Sn and HCl (27JCS116; 38JCS37). 2-Aminophenoxatellurine transforms under the usual conditions to its 2-diazo derivative, which on being coupled with 2-naphthole forms a deeply colored azo-dye (27JCS116). Peculiarly, however, the Sandmeyer reaction of 2-diazoniophenoxatellurine chloride with $CuCl$ results in not 2-chlorophenoxatellurine, but 2,10,10-trichlorophenoxatellurine (76RRC739). Evidently, the $Te(II) \rightarrow Te(IV)$ oxidation occurs under the action of $CuCl_2$ formed in the course of the reaction or under the action of HNO_2 during diazotization.

Although structural modifications of the basic phenoxatellurine and phenoxatellurazine derivatives have only been studied intermittently, interest grows in a more careful study of transformation of functional groups

in these heterocycles. This is initiated by communications (for example, see 66MI1; 78MI1; 82KFZ1070) concerning the strong antimicrobial properties of derivatives of phenoxatellurines and phenotellurazines.

5. Structure of Tricyclic Compounds in Crystal and in Solutions

Many X-ray structural investigations of type **92** heterocycles have been carried out with the exclusion of phenothiatellurine. Data on bond length and valency angles are given in Table VI.

Tricyclic compounds **92** have a butterfly conformation. In contrast to the corresponding monocyclic heterosystems (see Section IV,A,3,c) for which the chair conformation is preferred in **92** the six-membered heterocycle possesses a boat conformation. The dihedral angles of bending along the Te—M bonds depend on both the nature of the heteroatoms M and the electronegativity of the substituents at the tellurium center (80IC2556). Thus, whereas the dihedral angle for telluranthrene is 124°, for phenoxatellurine it is 145°. For 10,10-disubstituted phenoxatellurines **94** (M = O), the magnitudes of the dihedral angles between the planes of the two arene rings decrease in the order $\text{ONO}_2 > \text{I} > \text{OCOCF}_3 > \text{Cl}$, so that the molecule of phenoxatellurine 10,10-dinitrate **94** (M = O, X = ONO_2) is almost planar.

Not accounting for secondary bonds arising in crystals of compounds **94** due to shortened contacts between tellurium and halogen centers, the configuration of four-coordinated tellurium may be described as trigonal bipyramidal, the lone pair at tellurium being viewed as the phantom-ligand. In a crystal environment the coordination number of tellurium in

TABLE VI
BOND LENGTHS (Å) AND VALENCY ANGLES IN COMPOUNDS **92,94**

M	X	Bond lengths		Valency angles			Reference
		Te—C ^a	Te—X	C—Te—C	X—Te—X	Dihedral	
NEt ^b	—	2.106	—	89.8	—	137.7	85ZSK120
O	—	2.098	—	89.4	—	145.0	73JHC527
Te	—	2.115	—	95.6	—	124.0	81CSC1359
Te ^c	—	2.114	—	92.9	—	111.5	80JFC245
O	Cl	2.095	2.530	90.7	183.2	151.0	80IC2556
O	I	2.10	2.945	91.5	183.6	163.9	73IC2669
O	OCOCF ₃	2.066	2.20	91.5	192.5	156.0	73CSC629
O	ONO ₂	2.068	2.201	93.5	192.0	175.0	73JHC533

^a The mean values of bond lengths and valency angles are given.

^b Data for the 2,8-dimethyl-*N*-ethylphenotellurazine.

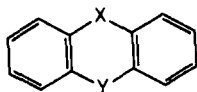
^c Data for the perfluorotellurantrene.

94 increases up to six and the configuration of bonds attached to it closely resembles octahedral one. The Te . . . Cl distances in a crystal of **94** (M = O, X = Cl) are found to lie in the range 3.368–3.504 Å (the sum of Van der Waals radii is 4.0 Å). The Te . . . I distances in a crystal of **94** (M = O, X = I) are 3.739–3.788 Å, the Van der Waals contact being equal to 4.35 Å.

Not only Te . . . I but also I . . . I intermolecular secondary bonds exist in a crystal, both of these providing for the alignment of chains of molecules **94** (M = O, X = I). Whereas (di(4-chlorophenyl)tellurium diiodide (62AX887) and 4,4-diiodo-1-thia-4-telluracyclohexane (70IC797) are dark-violet, crystals of 1,1-diiodo-3,4-benzo-1-telluracyclopentane [79JOM(178)423], 4,4-diiodo-1-oxa-4-telluracyclohexane (73IC2665), 1,1-diiododibenzotellurophene (75IC1142), and 10,10-diiodophenoxatellurine (73IC2669) span the spectral region from orange to red. These differences in color of diorganyl tellurium diiodides are said to be due to differences in the nature of the secondary bonds these molecules form in a crystal. Only for the first two deeply colored compounds do the I . . . I secondary bonds exist: Te . . . I bonds are characteristic of all the other compounds indicated above.

Special attention has been paid to the structure and spectral properties of heterocycles **92** and related systems in solution. The conformations of type **117** compounds were elucidated from their dipole moments [78JOM(146)235; 83JCS(P2)1109; 85ZOB846]. Some of the data are given in Table VII.

TABLE VII
DIPOLE MOMENTS (D) OF COMPOUNDS **117**
(BENZENE, 25°C)



X	Y	μ	Dihedral angle ^a
O	O	0.55	163.8
S	O	1.18	163.4
Se	O	0.73	162.6
Te	O	0.38	172.2
Te	Te	1.43	124.6
Se	Se	1.42	139.0
S	S	1.50	142.4

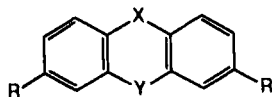
^a Values of dihedral angles at which the calculated dipole moments coincide with experimental values are given.

The conformation of the tricyclic compounds of type **117** is determined by two opposing factors: π -conjugation favoring planarity and steric constraints leading to puckering of the heterorings. In solution compounds **117** retain the butterfly conformation proved by X-ray crystal studies, although the magnitudes of the dihedral angles determined by dipole moment measurements are 20–30° greater than those found in the crystalline state. An exception is benzo-*p*-dioxine, which is planar in the crystalline state (73CSC311), whereas the nonzero value of its dipole moment indicates a bent molecular conformation. It should, however, be kept in mind that structural assignment made on the grounds of a low dipole moment requires an especially careful estimation or preferably direct experimental determination of the atomic polarization, not available in the case in these dipole moment measurements.

The nonplanar structure of tricyclic compounds **117** has also been confirmed by photoelectron spectral studies [78JOM(146)235; 83JCS(P2)1109]. Data on the ionization potentials and the UV-absorption spectra of these compounds [70RRC501; 78JOM(146)235; 83JCS(2)1109] are given in Table VIII.

The energies of the first two highest occupied molecular orbitals of **117** depend little on the nature of the chalcogene, although in the case of planar conformations their magnitudes should have decreased passing

TABLE VIII
IONIZATION ENERGIES AND UV SPECTRA (HEPTANE)
OF



R	X	Y	<i>I</i> (ev)	λ_{\max}
H	O	O	7.78, 8.76, 9.5, 9.7, 11.24, 12.20	203 w, 222, 228, 289 300 sh
H	O	S	7.72, 8.71, 9.4, 9.6, 10.63, 11.13, 11.7	220 w, 238, 241, 295 sh
H	O	Se	7.74, 8.67, 9.33, 9.5, 10.33, 10.9, 11.5	202, 218, 238, 241, 294
H	O	Te	7.61, 8.66, 9.24, 9.4, 9.94, 10.45, 11.3, 11.4	202, 230, 257, 290, 356
Me	O	Te	—	240, 260, 298, 358
Cl	O	Te	—	244, 262, 302, 357
H	Te	Te	7.52, 7.72, 9.12, 9.30, 9.79, 10.22, 10.51, 10.83	—

from dibenzo-*p*-dioxine to phenoxatellurine. But deviation from planarity reduces not only the π -conjugation of the chalcogene lone pair with the benzene ring orbitals but also the ring strain. According to Distefano *et al.* [78JOM(146)235; 83JCS(P2)1109] this leads to an approximate constancy in the energy levels of the two highest occupied molecular orbitals of tricyclic compounds **117**.

The data on the electron distribution in molecules **117** were obtained with the use of ^1H NMR (71AJC325; 73RRC531) and ^{13}C NMR [79JOM(181)329; 81JOM(212)141; 89H1007] studies. Some results are presented in Table IX.

Noteworthy is the significant difference in magnitude of the chemical shifts of the C-6 nuclei bound to the chalcogenes. The replacement of the oxygen atoms in dibenzo-*p*-dioxine by sulfur, selenium, or tellurium results in upfield shifts by 22.2, 26.6, and 40.1 ppm, respectively. This may be explained by the inductive effect of the chalcogenes as well as by anisotropic effect of the chalcogene atoms which is largest in the case of tellurium. The chemical shifts of the C-5 nucleus in **117**, unlike those of C-6, exhibit downfield shifts increasing in the order O, S, Se, Te. This is probably caused by the fact that the σ -inductive effect of the oxygen atom overcomes the π -donating effects exerted by the chalcogene atoms, the latter decreasing in the order S, Se, Te. The chemical shifts of the C-1, C-2, C-3, and C-4 nuclei in **117** are also downfield compared to those of dibenzo-*p*-dioxine, the largest relative shifts being shown by the C-1 nuclei.

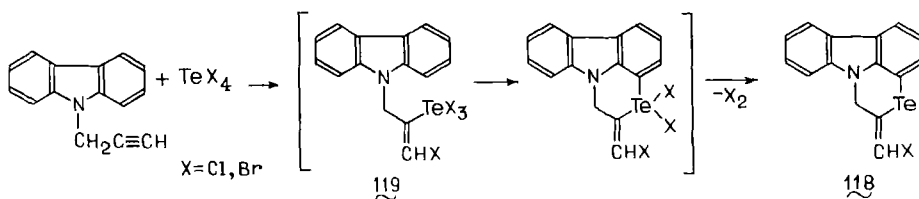
The ^{125}Te chemical shifts in **117** span a wide range of values, 293.6 ppm for phenotellurazine, 424 ppm in phenoxatellurine (89H1007), and 888 ppm in telluranthrene [81JOM(212)141], relative to Me_2Te .

TABLE IX
 ^{13}C CHEMICAL SHIFTS OF COMPOUNDS **117** (CDCl_3)

		Chemical shifts (δ , ppm)					
X	Y	C-1	C-2	C-3	C-4	C-5	C-6
O	O	116.2	123.6	123.6	116.2	142.1	142.1
O	S	127.4	124.3	126.5	117.5	161.9	119.9
O	Se	129.2	124.8	128.0	118.5	152.8	116.1
O	Te	134.8	125.4	128.9	119.5	155.6	102.0
NH	Te	135.0	123.7	128.5	116.2	144.5	97.7
Te	Te	136.5	128.3	128.3	136.5	130.6	130.6

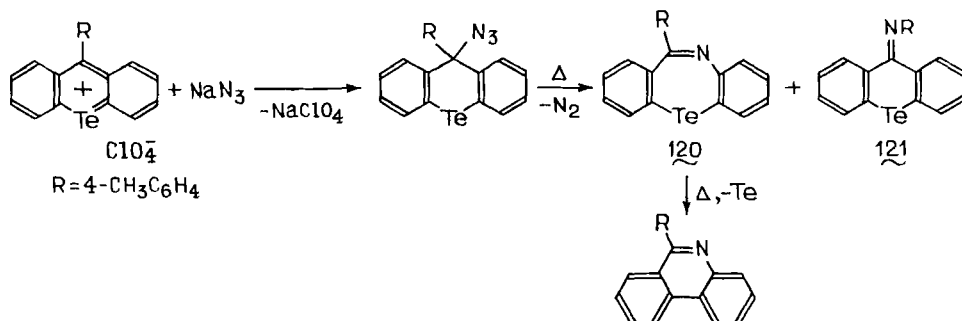
V. 1,4-Tellurazino[2,3-*g,h*]carbazoles

Thus far only two representatives of this heterocyclic system have been described in the literature. 2-Halohenomethylidene-1,4-tellurazino[2,3-*g,h*]carbazoles **118** were obtained in 39–48% yield through spontaneous intramolecular electrophilic cyclization of compounds **119** with subsequent or simultaneous elimination of halogens (90KGS126). This transformation was realized as a one-pot reaction when *N*-propargylcarbazole was treated by tellurium tetrahalogenides under the conditions of a double-phase tellur-ohalogenation reaction. Such an elimination of halogen is known as one of the steps of the synthesis of benzo[*b*]tellurophenes [79TL1509; 80JOM(199)377].



VI. Seven-Membered Heterocycles

Of seven-membered tellurium-containing heterocycles only 11-(*p*-tolyl)-dibenzo[*b,f*][1,4]telluroazepine **120** is known (87KGS279). This compound has been synthesized by an analogy based on reactions used for the synthesis of its sulfur and selenium congeners (76TL3141; 84JHC1321). When a *p*-xylene solution of 9-azido-9-(*p*-tolyl)telluroxanthene is heated at 130–140°C, a nitrogen molecule is eliminated and **120** is formed in 21% yield along with telluroxanthene imine **121** (32%) and a small amount of phenanthridine. The latter is the product of an extrusion of tellurium from



120 as may be inferred from the fact that an extrusion of selenium from dibenzoselenazepine takes place under similar conditions (84JHC1321). The initial axide was prepared in high yield by treatment of telluroxanthylum perchlorate (81KGS343) and with sodium azide.

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Reactions of Coordinated Ligands

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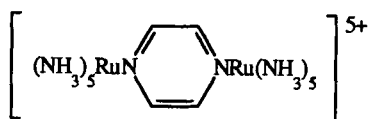
I. Introduction

Coordination of a ligand to a metal ion has long been known to alter its chemical properties. As early as 1856 Gibbs and Genth demonstrated that the oxalate ligands of $[\text{Co}(\text{ox})_3]^{3-}$ were not oxidized by HAuCl_4 , in contrast to the behavior of the free acid (87M11). Oxidation of the coordinated thiocyanate in $[\text{Co}(\text{NH}_3)_5(\text{NCS})]^{2+}$ to give $[\text{Co}(\text{NH}_3)_6]^{3+}$ by Werner and the reduction of the nitro ligand of $[\text{Pt}(\text{en})(\text{NH}_3)(\text{NO}_2)]^+$ giving $[\text{Pt}(\text{en})(\text{NH}_3)_2]^{2+}$ are two other early examples of ligand reactions where reaction is greatly facilitated by coordination to a transition metal (63M11). Coordination of a ligand to a transition metal will perturb both the d orbitals of the metal and the molecular orbitals of the ligand via a combination of electronic and steric effects, and these interactions can significantly alter the reactivity of the bound ligand relative to its free counterpart. Coordination involves transfer of electron density from a filled ligand orbital to a metal orbital of suitable symmetry and two possibilities exist for this process. Bonding in the so-called "classical" coordination complexes involves σ -donation of a lone pair of electrons from the ligand to the

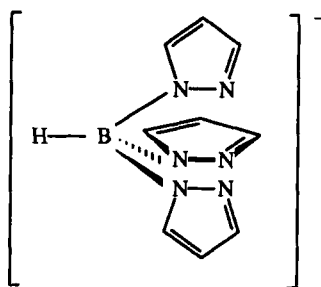
metal, whereas π -electron donation from ligand to metal is important in organometallic complexes containing unsaturated ligands. In both cases, consideration of these effects alone would predict the ligand to be more electrophilic due to polarization by the metal ion and this has indeed been observed for many systems. However, the electronic properties of the metal ion are also important in determining the reactivity of the bound ligand. The metal ion may contain empty d -orbitals that can receive electron density from ligand orbitals of suitable symmetry and energy, thereby enhancing the electrophilicity of the ligand as discussed above. Conversely, the metal ion may donate electron density from filled d -orbitals to suitable empty ligand orbitals, thus opposing and possibly outweighing ligand-to-metal σ -donation and leading to an increase in the nucleophilicity of the ligand. Coordination of a heterocycle to a transition metal ion via σ -donation of an electron pair from the heteroatom will remove its basic properties, effectively blocking such reactions as protonation and alkylation at this site and possibly leading to reaction elsewhere in the ring.

In addition to these electronic effects, coordination to a metal ion also introduces steric constraints that are not present in the free ligand. Consequently ligand atoms adjacent to the metal ion will be sterically hindered and reactivity at these sites may be reduced or indeed totally eliminated. In cases where the ligand exists as a tautomeric mixture, metal coordination can "freeze" the ligand in one tautomeric form, thereby allowing the reactivity of separate tautomers to be studied. It is also frequently observed in transition metal complexes that a bound ligand will adopt a different conformation to that of the free species and this effect can again be manifested in reactivity differences (88MI2). Thus through a combination of steric and electronic factors, bound ligands are often found to behave quite differently from their unbound congeners. Such differences have been the basis of numerous investigations that have themselves been well reviewed (63MI1; 64JCE493; 66MI1; 87MI2; 90MI1).

The chemistry of metal-heterocycle complexes has been extensively studied in recent years (78JHC1057; 87MI3) and recent reviews of transition metal-heterocycle systems are listed at the end of this chapter. Of particular note among these studies is the photochemistry of the $[\text{Ru}(\text{bpy})_3]^{2+}$ cation and related systems, which have long been and remain a source of intense interest owing to the long-lived excited state formed on irradiation, which shows promising catalytic properties. The electronic structure of the mixed-valence pyrazine-bridged complex $[(\text{NH}_3)_5\text{Ru}(\text{pz})-\text{Ru}(\text{NH}_3)_5]^{5+}$ (**1**) (the Creutz-Taube ion) and mediation of electron-transfer by bridging heterocycles of this type are also examples of much studied metal heterocyclic systems. The tris(pyrazolyl)borate ion (**2**) is but one of numerous polydentate heterocyclic ligand systems that have been syn-



(1)



(2)

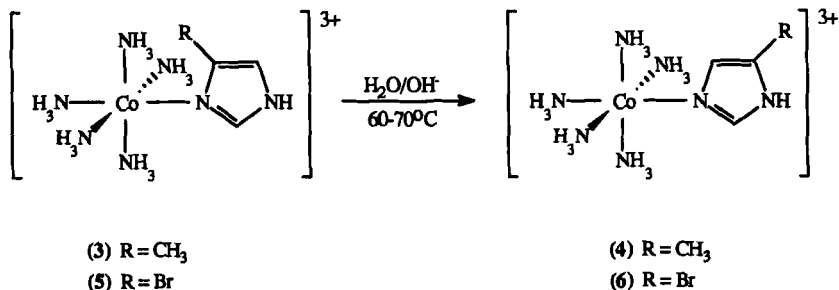
thesized. This ligand and its derivatives have been found to act as facially coordinating tridentate ligands to a large number of transition metal ions and many novel complexes have been prepared. However, in most transition metal–heterocycle systems the emphasis has been on either the synthesis and structure of these complexes or their unusual physical properties. The reactions of the bound heterocycles themselves have been little investigated and the possible synthetic utility of such reactions is only now beginning to be realized. The purpose of this chapter is to review the reactions of transition metal-bound aromatic heterocycles, focusing on the ways in which metal coordination affects the reactivity of the bound heterocycle in comparison to that of the free ligand. Heterocycles containing less common heteroatoms will not be covered, although the interested reader is referred to Mathey's extensive work with transition metal-bound phospholes (see under Recent Reviews of Related Topics). The chapter is limited to the reactions of discrete, well-characterized transition metal–heterocycle complexes and papers in which ligand transformations occur via putative metal-bound heterocyclic intermediates have been omitted.

II. Modes of Binding

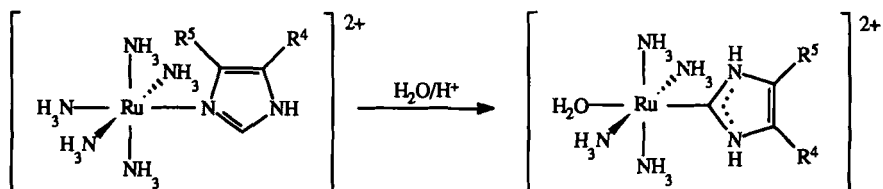
Heterocycles can coordinate to transition metals by either σ - or π -electron donation from ligand to metal. The former most commonly occurs via the heteroatom, although binding through a ring carbon atom has often been observed, most notably in cyclometallated complexes (84M17). π -coordination almost always requires the metal ion to be in a low oxidation state and can utilize either all or part of the π -system. Thus any given heterocycle will have a number of coordination modes open to it and synthesis of the metal complex can result in isolation of the kinetic product,

which can then undergo isomerization to give the thermodynamic product. A number of these reactions have been studied.

Coordination of 4(5)-methylimidazole to $\text{Co}(\text{NH}_3)_5^{3+}$ gave a mixture of the 4- and 5-substituted isomers in which the substituent was situated adjacent to (5-isomer)(3) or remote from (4-isomer)(4) the ammonia ligands on the metal ion. The sterically hindered adjacent isomer was found to undergo an intramolecular isomerization on heating to give the remote isomer as the thermodynamic product (Scheme 1). Rate data were consistent with reaction via both the imidazole 3 + and deprotonated imidazolate 2- forms of the complex (83IC2693). A similar isomerization has been observed for the adjacent monobromoimidazole complex $[\text{Co}(\text{NH}_3)_5(5\text{-BrimH})]^{3+}$ (5), which was formed exclusively from the 4(5)-bromoimidazole ligand and gave the 4-bromoimidazole complex (6) on heating. In this case, a kinetic study suggested reaction solely via the conjugate base imidazolato form [91JCS(D)3031]. A mechanism involving a π -bound intermediate was suggested for both transformations. The reaction of L-histidine with $[\text{Fe}(\text{CN})_5(\text{OH}_2)]^{3-}$ in mixed water/DMSO solvent gave coordination via both N-1 and the more sterically hindered N-3 atom of the imidazole ring, whereas under basic conditions, coordination of the primary amine was also observed. A kinetic study of the postulated isomerization of the N-3- and NH_2 -bound species to the more stable N-1 isomer was complicated by the lability of the iron-histidine complexes [78JCS(D)1610]. An unusual N-bound to C-bound rearrangement of the imidazole ligand was observed on acidification of aqueous solutions of the N-bound Ru(II) complexes $[\text{Ru}(\text{NH}_3)_5\text{L}]^{2+}$ [L = imidazole (7), 4,5-dimethylimidazole (8), histidine (9)]. This was also accompanied by aquation to give the *trans*- $[\text{Ru}(\text{NH}_3)_4(\text{H}_2\text{O})\text{L}]^{2+}$ species in which the imidazole ligand is bound via C-2 as an imidazolium ylide (Scheme 2). The isomerization was found to be first-order in $[\text{H}^+]$ and an intramolecular mechanism was suggested (82IC3361).

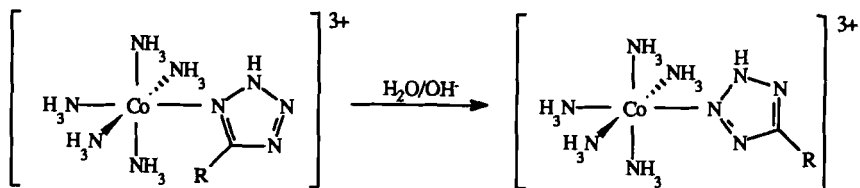


SCHEME 1

(7) $R^4 = R^5 = H$ (8) $R^4 = R^5 = CH_3$ (9) $R^4 = CH_2CH(NH_2)(COOH)$, $R^5 = H$

SCHEME 2

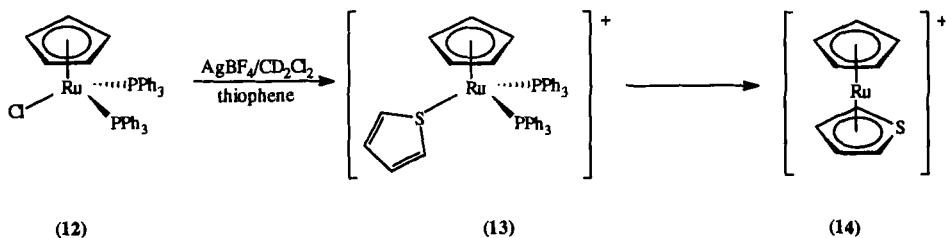
The preparation of the tetrazole complexes $[Co(NH_3)_5(5-R\text{-tetrazole})]^{3+}$ [$R = \text{methyl (10)}$, phenyl (**11**)] by reaction of azide ion with the appropriate metal-coordinated nitrile in aqueous solution was found to initially give the 5-substituted (adjacent) complex, which then isomerized to the less sterically demanding 4-substituted (remote) species (Scheme 3). The phenyltetrazole complex reacted faster than its methyl-substituted congener, consistent with the driving force of the reaction being relief of steric congestion. This process was suggested to occur by an intramolecular mechanism, as no aquation product ($[Co(NH_3)_5OH_2]^{3+}$) was observed (82IC834). A kinetic study of the isomerization of the 5-methyl complex (**10**) in water found both the $3+$ and the deprotonated $2+$ forms to be reactive, with rate constants for the $3+$ being larger by approximately two orders of magnitude. A base-catalyzed path was also observed at high pH values and this was attributed to deprotonation of an ammine ligand prior to isomerization (83IC1205). Reaction of the deprotonated $2+$ complex was studied in a variety of nonaqueous solvents and rate constants

(10) $R = CH_3$ (11) $R = C_6H_5$

SCHEME 3

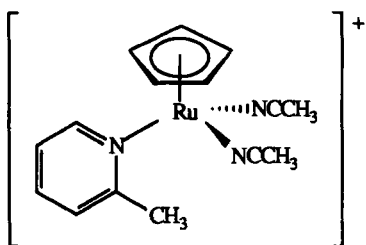
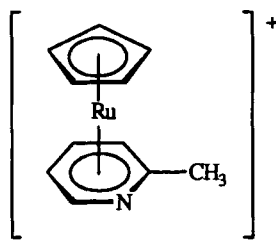
for this were found to be slower than the corresponding process in water. A correlation between the rate constants and the Reichardt (E_T) and Gutmann (D_N) solvent parameters was found and the Kamlet and Taft equation could also be used to model the solvent effects. These observations were used as evidence of a tight ion-pair transition state that is little affected by electronic properties of the solvent (91IC3707). Rate data for the reaction of a number of 5-(R-phenyl)tetrazole complexes ($R = 4\text{-Me}$, 4-H , 4-Cl 3-CF_3 , 4-NO_2) in water showed a pH profile similar to that of the 5-methyl complex with reaction through the protonated $3+$ species again being more rapid. The nature of the substituent on the phenyl ring affected the rate of the isomerization, electron-withdrawing substituents giving greater rate constants that were found to correlate with the Hammett σ -parameter (90IC3806).

Aromatic heterocyclic ligands are potentially ambidentate and several cases of isomerization between π - and σ -bonding modes have been documented. The reaction of a dichloromethane solution of $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{PPh}_3)_2\text{Cl}]$ (**12**) with AgBF_4 in the presence of thiophene gave a thermally unstable compound that was suggested on the basis of NMR evidence to be the S-bound complex $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\text{PPh}_3)_2(\text{S-thiophene})]^+$ (**13**). On standing in solution this species reacted to give the η^5 -bound complex $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)(\eta^5\text{-thiophene})]^+$ (**14**) (Scheme 4) (85M12). A similar S-bound to π -bound linkage isomerization was observed in the complexes $[\text{M}(\eta^5\text{-C}_5\text{Me}_5)(\text{S-dibenzothiophene})\text{Cl}_2]$ ($\text{M} = \text{Rh}, \text{Ir}$), where heating a nitromethane solution in the presence of AgBF_4 gave the corresponding η^6 -bound species. This process could be reversed by addition of NEt_4Cl (91IC5046). Coordination of benzo[*b*]thiophene to the $[\text{Re}(\eta^5\text{-C}_5\text{R}_5)(\text{CO})_2]$ ($\text{R} = \text{H}, \text{Me}$) fragment gave an equilibrium mixture of the π η^2 -bound and the σ S-bound isomers. Kinetic data for the π - σ interconversion showed the C_5H_5 complex to isomerize to the S-bound isomer approximately eight times more rapidly than its C_5Me_5 congener and the reaction was suggested to occur intramolecularly, as no exchange of the ligand with added 2-methylbenz[*b*]thiophene was observed (91JA4005).



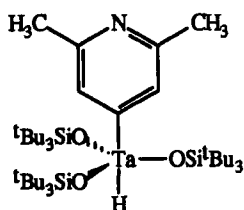
SCHEME 4

Fish and co-workers have studied N-to- π rearrangements of a number of cyclopentadienyl rhodium and ruthenium complexes of pyridines and quinolines. This behavior was first observed in the complex $[\text{Ru}(\text{C}_5\text{H}_5)(\text{CH}_3\text{CN})_2(2\text{-Mepy})]^+$ where the σ -bound N-isomer (**15**) gave an equilibrium mixture of the N- and π -bound (**16**) complexes on heating in 1,2-dichloroethane (ratio **15**:**16** = 6:1). No free ligand was detected in

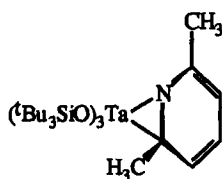
**(15)****(16)**

the equilibrium mixture and no isomerization reaction was observed with the unsubstituted N-bound pyridine complex under the same conditions. The corresponding quinoline complex also underwent an N-to- π rearrangement, but in this case the heterocyclic ligand of the $[\text{Ru}(\text{C}_5\text{H}_5)(\text{quinoline})]^+$ product is η^6 -bound to the metal ion via the benzene ring. Again, no free ligand was observed, indicating an intramolecular process (89MI1). Replacement of C_5H_5 with C_5Me_5 caused marked changes in reactivity and in this case the N-to- π rearrangement was observed for the unsubstituted N-bound pyridine complex, whereas the attempted preparation of the N-bound 2-methylpyridine and quinoline complexes gave only the η^6 -bound isomers, which were presumably formed via the intermediacy of the N-bound species in a process that was too fast to observe. The enhanced reactivity of these C_5Me_5 complexes was ascribed to the superior electron-donating properties of the C_5Me_5 ring, which render the metal center a better π -donor, thus allowing stabilization of the η^6 bonding mode (91MI4). Mechanistic studies of the reactions of the C_5H_5 complexes showed both the N- and the π -bound heterocycles to undergo facile exchange with free ligand and this precluded unequivocal assignment of an intramolecular mechanism (91MI2). The Rh(III) complex $[\text{Rh}(\text{C}_5\text{Me}_5)(\text{acetone})_2(2\text{-methylquinoline})]^2+$ was also found to undergo the same N-to- π rearrangement on vacuum-drying, with the product again showing η^6 -bonding of the heterocycle via the benzene ring (91MI5). An interesting σ - to π -ligand isomerization has been observed in the complex $[\text{Ta}(t\text{-Bu}_3\text{Si-}$

$O)_3(H)(2,6-Me_2py)]$ (17) in which the 2,6-lutidine ligand is bound via C-4. On standing in C_6D_6 solution for 3-4 days, this reacted to give an equilibrium mixture of starting material, free 2,6-lutidine, and the η^2 -bound complex $[Ta(t-Bu_3SiO)_3(\eta^2-2,6-Me_2py-N,C)]$ (18) where the lutidine ligand is now bound "side-on" to the metal. This same bonding geometry was observed in the sterically unhindered pyridine complex but attempts at conversion to the N-bound species failed (91IC2494).



(17)



(18)

III. Acidity Constants

The acid/base properties of metal-coordinated heterocycles have been extensively studied to determine the effect of metal coordination upon the electronic structure of the heterocycle. The pK_a values of a number of transition-metal heterocycle complexes are given in Table I along with data (where available) for the free ligand. σ -coordination of a heterocycle via the heteroatom removes its acid/base properties and thus σ -bound pyridine and pyrrole complexes are not amenable to study. However, π -coordination of these ligands leaves the heteroatom free for protonation/deprotonation and, although this is a relatively rare mode of coordination, several studies of the acid/base chemistry of such complexes have been made. The pK_a of the Cr(0) complex $[Cr(\eta^6-C_5H_5NH)(\eta^6-C_6H_6)]^+$ (19) has been found to be some 2.5–3 pK_a units greater than free pyridine and this is consistent with significant electron donation from the metal d -orbitals to unoccupied antibonding orbitals of the pyridine ligand (88CB1983). The opposite effect is seen in the complex $[Fe(\eta^5-C_5H_5)(\eta^5-C_4Me_4NH)]^+$ (20) in which the pyrrole ligand is π -bound to the metal ion. The pK_a of this complex is 7.2, a decrease of some 10 pK_a units over the free ligand, suggesting that in this case the metal ion is acting as a strong Lewis acid, with little or no involvement of the metal d -orbitals in $d-\pi^*$ backbonding (89CB1891). Pyrrole can also coordinate to $Os(NH_3)_5^{2+}$ in an η^2 fashion

TABLE I
pKa VALUES OF TRANSITION METAL HETEROCYCLE COMPLEXES

Complex	pKa	pKa of free ligand	Reference
[Co(imH) ₆] ³⁺	8.65, 9.88, 10.63	14.4	89IC1405
Aquocobalamin (imH)	9.85		90MI2
[Co(en) ₂ (H ₂ O)(imH)] ³⁺	10.5 (30.0°C)		84IC891
	10.5		
	10.7 (22.0°C)		
	10.7 (16.0°C)		
[Cr(NH ₃) ₅ (imH)] ³⁺	9.35		88IC1086
[Rh(NH ₃) ₅ (imH)] ³⁺	10.88 (0°C)		84IC1851
	9.97		
	9.79 (30.0°C)		
	9.57 (40.0°C)		
	9.28 (50.0°C)		
	8.92 (60.0°C)		
	8.62 (70.0°C)		
[Ru(NH ₃) ₅ (imH)] ³⁺	8.9		74JA381
[Co(CN) ₅ (imH)] ²⁻	11.4		84IC1851
[Ir(NH ₃) ₅ (imH)] ³⁺	10.94 (0.0°C)		84IC1851
	10.05		
	9.84 (30.0°C)		
	9.64 (40.0°C)		
	9.33 (50.0°C)		
	8.99 (60.0°C)		
	8.75 (70.0°C)		
[Co(NH ₃) ₅ (imH)] ³⁺	10.02		76JA7282
	9.92 (30.0°C)		91JCS(D)3031
	9.82 (35.0°C)		
	9.62 (40.0°C)		
[Co(NH ₃) ₅ (2,4,5- <i>d</i> ₃ -imH)] ³⁺	10.04		91JCS(D)3031
[Fe(CN) ₅ (imH)] ²⁻	11.00 (21.2°C)		80JA6227
	10.93 (26.0°C)		
	10.85 (30.2°C)		
	10.68 (38.4°C)		
[Ru(NH ₃) ₅ (imH ₂)] ³⁺ (bound via C-2)	11.0	6.99	82IC3361
Microperoxidase-8 (axial imidazole)	13.0	14.4	90IC1597
Aquocobalamin (4-MeimH)	10.43	15.1	90MI2
[Co(en) ₂ (H ₂ O)(4-MeimH)] ³⁺	10.6 (30.0°C)		84IC891
	10.8 (26.0°C)		
	11.1 (15.0°C)		
[Co(NH ₃) ₅ (4-MeimH)] ³⁺	10.70		83IC2693
	10.37 (35.0°C)		
	10.18 (40.0°C)		

(continued)

TABLE I (Continued)

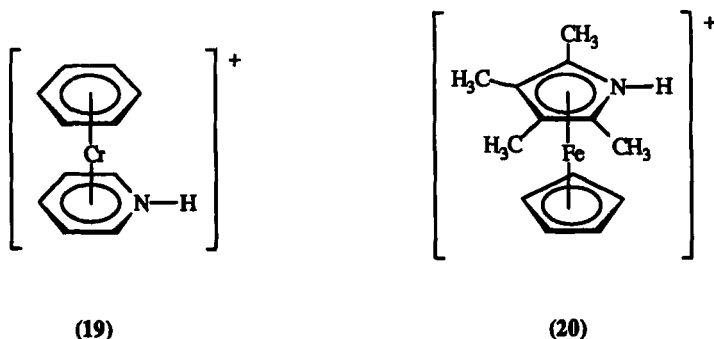
Complex	pKa	pKa of free ligand	Reference
	9.91 (50.0°C)		
	9.62 (60.0°C)		
	9.41 (65.0°C)		
	9.20 (70.0°C)		
	9.06 (75.0°C)		
	8.95 (80.0°C)		
$[\text{Co}(\text{NH}_3)_5(5\text{-MeimH})]^{3+}$	10.46	15.1	83IC2693
	10.05 (35.0°C)		
	9.85 (40.0°C)		
	9.50 (50.0°C)		
	9.09 (60.0°C)		
	8.87 (65.0°C)		
	8.67 (70.0°C)		
	8.47 (75.0°C)		
	8.27 (80.0°C)		
$[\text{Ru}(\text{NH}_3)_5(5\text{-MeimH})]^{3+}$	9.0		74JA381
$[\text{Cr}(\text{NH}_3)_5(2\text{-MeimH})]^{3+}$	10.20	15.1	88IC1086
$[\text{Co}(\text{NH}_3)_5(2\text{-MeimH})]^{3+}$	10.67		84IC1851
$[\text{Co}(\text{NH}_3)_5(2,4\text{-Me}_2\text{imH})]^{3+}$	11.04	—	84IC1851
$[\text{Ru}(\text{NH}_3)_5(2,4\text{-Me}_2\text{imH})]^{3+}$	10.20		84IC1851
$[\text{Ru}(\text{NH}_3)_5(4,5\text{-Me}_2\text{imH})]^{3+}$	9.5	—	74JA381
$[\text{Co}(\text{NH}_3)_5(4\text{-BrimH})]^{3+}$	8.06	12.16	91JCS(D)3031
$[\text{Co}(\text{NH}_3)_5(5\text{-BrimH})]^{3+}$	6.38	12.16	91JCS(D)3031
$[\text{Co}(\text{NH}_3)_5(4,5\text{-Br}_2\text{imH})]^{3+}$	4.69	—	91JCS(D)3031
$[\text{Co}(\text{NH}_3)_5(2,4,5\text{-Br}_3\text{imH})]^{3+}$	1.83	—	91JCS(D)3031
$[\text{Co}(\text{NH}_3)_5(4\text{-NO}_2\text{imH})]^{3+}$	1.66	9.30	83IC678
$[\text{Fe}(\text{CN})_5(4\text{-NO}_2\text{imH})]^{3-}$	6.8		85IC1424
Aquocobalamin (histamine)	9.89	—	90MI2
Aquocobalamin (histidine)	10.06	14.37	90MI2
$[\text{Co}(\text{en})(\text{H}_2\text{O})(\text{histidine})]^{2+}$	10.7 (35.0°C)		84IC891
	10.8 (30.0°C)		
	10.8		
	10.9 (20.0°C)		
$[\text{Co}(\text{NH}_3)_2(\text{glyglyhis})]$	9.81	—	83IC3879
$[\text{Ru}(\text{NH}_3)_5(\text{bzimH})]^{3+}$	7.2	12.86	74JA381
$[\text{Ru}(\text{NH}_3)_5(\text{biimH}_2)]^{3+}$	5.65	11.5	86MI1
$[\text{Cr}(\text{NH}_3)_5(\text{pyzH})]^{3+}$	6.71	14.21	88IC1086
$[\text{Ru}(\text{NH}_3)_5(\text{pyzH})]^{3+}$	5.98		84IC2754
$[\text{Co}(\text{NH}_3)_5(\text{pyzH})]^{3+}$	6.07		84IC2754
$[\text{Co}(\text{CN})_5(\text{pyzH})]^{2-}$	10.9		84IC2754
$[\text{Co}(\text{NH}_3)_5(3\text{-MepyzH})]^{3+}$	6.7	14.54	84IC2754
$[\text{Ru}(\text{NH}_3)_5(3\text{-5-Me}_2\text{pyzH})]^{3+}$	7.21	15.00	84IC2754
$[\text{Ru}(\text{NH}_3)_5(1,2,4\text{-triazoleH})]^{3+}$	4.3	10.04	84IC2754

(continued)

TABLE I (Continued)

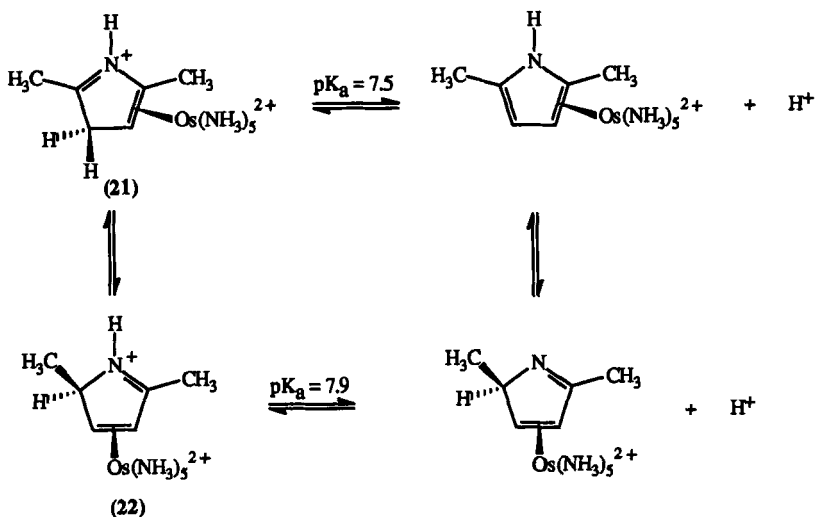
Complex	pKa	pKa of free ligand	Reference
[Co(NH ₃) ₅ (5-methyltetrazoleH)] ³⁺ (bound via N-1)	1.66 (14.3°C)	5.63	83IC1205
	1.52		
	1.57 (48.3°C)		
	1.57 (63.3°C)		
[Co(NH ₃) ₅ (5-(R-phenyl)tetrazoleH)] ³⁺			
R = H	0.59, 0.80	4.98	90IC3806
R = 4-CH ₃	0.84, 0.89	5.17	
R = 4-Cl	0.39, 0.57	4.49	
R = 3-CF ₃	-0.04, 0.21	—	
R = 4-NO ₂	0.26, -0.34	3.69	
[Cr(η ⁶ -C ₆ H ₅ NH)(η ⁶ -C ₆ H ₆)] ⁻	7.7, 8.2	5.21	88CB1983
[Ru(NH ₃) ₅ (pzH)] ³⁺	2.5	0.65	68JA1187
[Ru(NH ₃) ₅ (pzH)] ⁴⁺	-0.8		68JA1187
[Os(NH ₃) ₅ (pzH)] ³⁺	7.4		79ACS(A)125
[Ru(CN) ₅ (pzH)] ²⁻	0.4		83IC1117
<i>trans</i> -[Ru(NH ₃) ₄ (4-pic)(pzH)] ³⁺	2.1		88IC3410
<i>trans</i> -[Ru(NH ₃) ₄ (isn)(pzH)] ³⁺	1.6		88IC3410
<i>trans</i> -[Ru(NH ₃) ₄ (4-acpy)(pzH)] ³⁺	1.5		88IC3410
<i>trans</i> -[Ru(NH ₃) ₄ (py)(pzH)] ³⁺	2.0		80IC72
<i>trans</i> -[Ru(NH ₃) ₄ (pz)(pzH)] ³⁺	1.5		80IC72
<i>trans</i> -[Ru(NH ₃) ₄ (pzH) ₂] ⁴⁺	-0.6		80IC72
<i>cis</i> -[Ru(NH ₃) ₄ (isn)(pzH)] ³⁺	1.7		85IC4444
<i>cis</i> -[Os(NH ₃) ₄ (Cl)(pzH)] ²⁺	7.6		75JA5129
<i>cis</i> -[Os(NH ₃) ₄ (N ₃)(pzH)] ³⁺	0.31		75JA5129
[Ru(NH ₃) ₅ (dmpzH)] ³⁺	3.70 (15.0°C)	1.9	85IC3085
	3.55		
	3.40 (35.0°C)		
[Fe(CN) ₅ (dmpzH)] ²⁻	2.80		85IC3085
[Fe(CN) ₄ (HCN)(dmpzH)] ⁻	1.5		85IC3085
[Ru(CN) ₅ (dmpzH)] ²⁻	1.90		85IC3085
[Ru(CN) ₄ (HCN)(dmpzH)] ⁻	< 1		85IC3085
[Os(NH ₃) ₅ (pyridazineH)] ³⁺	3.7	2.33	79ACS(A)125
[Ru(NH ₃) ₅ (pyridazineH)] ³⁺	0.03		68JA1187
[Os(NH ₃) ₅ (pyridazineH)] ³⁺	2.1	1.3	79ACS(A)125
[Ru(NH ₃) ₅ (4,4'-bpyH)] ⁴⁺	4.4	4.9	72JA2583

Note. Abbreviations used: imH, imidazole; imH₂, neutral imidazolium ylide (deprotonated at C-2); glyglyhis, glycyglycyl-L-histidine; bzimH, benzimidazole; biimH₂, 2,2'-biimidazole; pyzH, pyrazole; pz, pyrazine; pzH, pyrazinium monocation; 4-pic, 4-picoline; isn, isonicotinamide; py, pyridine; 4-acpy, 4-acetylpyridine; dmpzH, 2,6-dimethylpyrazinium monocation; 4,4'-bpyH, 4,4'-bipyridinium monocation. *T* = 25°C unless otherwise stated.



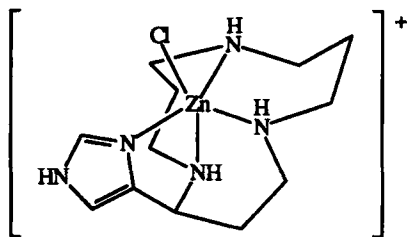
and the pK_a values of a number of these complexes have been measured (92JA5684). In this case, π metal coordination imparts enamine character to the heterocycle, enabling facile protonation at the β -carbon as shown in Scheme 5 for the 2,5-dimethylpyrrole complex. The protonated species (21) (pK_a 7.5) undergoes isomerization to give an α -protonated complex (22) where the $Os(NH_3)_5^{2+}$ moiety is now η^2 -bound to the heterocycle via C-3 and C-4. This species may be deprotonated at nitrogen (pK_a 7.9).

The pK_a values of azoles σ -bound to transition metals have been extensively studied for a variety of reasons. The acidity of a proton on a heterocycle bound to a transition metal is very sensitive to the electronic properties of the metal ion and numerous studies of these complexes



SCHEME 5

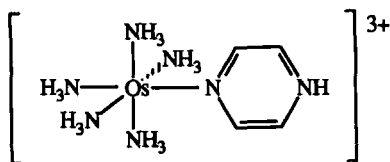
have given great insight into the importance of π -backbonding effects in complexes of the heavier transition metals. Metal-binding to imidazole-containing histidine residues is important in a number of metalloproteins and model studies of simple M^{3+} -imidazole complexes have been made to determine the effect of metal coordination on the acid/base properties of the imidazole ring. These studies have shown the pK_a of imidazole and various substituted imidazoles to be substantially lowered (by 4–6 pK_a units, Table I) on coordination to L_5M^{3+} systems ($M = Cr, Co, Ru, Rh, Ir$), reflecting σ -electron donation from ligand to metal, which leads to stabilization of the conjugate base form of the ligand. Such effects are undoubtedly important in biological systems, where metal coordination would allow the potentially nucleophilic imidazolite conjugate base to exist in significant amounts at relatively low pH values. Indeed, deprotonated $[Co(NH_3)_5im]^{2+}$ has been found to be more effective at promoting the cleavage of 4-nitrophenylacetate in water than the hydroxo complex $[Co(NH_3)_5OH]^{2+}$ (76JA7282). Similarly the Cu(II) imidazolite complex $[Cu(dien)(im)]^+$ (dien = diethylenetriamine) cleaves the ester bond of 4-nitrophenylbenzoate in DMSO more effectively than sodium imidazolite. Under these conditions, the activities of the imidazole complex $[Cu(dien)(imH)]^{2+}$, the N-ethylimidazole complex $[Cu(dien)(1-Etim)]^{2+}$, and free imidazole were zero (87CC839). Both studies ascribed the reactivity of the conjugate base form of the complexes to the nucleophilicity of the electron pair located on the deprotonated nitrogen atom. The metalloenzyme carbonic anhydrase contains a Zn(II) ion bound to both histidine imidazole and water and shows a pK_a of ~ 7 . This is unlikely to be due to a zinc-coordinated imidazole, as a model study of the Zn(II)-imidazole complex $[Zn(2-(4\text{-imidazolyl})-1,5,9\text{-triazacyclododecane})Cl]^+$ (**23**) shows a pK_a ascribed to the imidazole proton of 10.3. This has been used as further evidence against the operation of the so-called "zinc-imidazolite" catalytic mechanism with the observed deprotonation in the enzyme being ascribed to a coordinated water molecule (91IC4524). Interestingly, **23**



(23)

did not promote hydrolysis of 4-nitrophenylacetate, in contrast to $[\text{Co}(\text{N-H}_3)_5\text{imH}]^{3+}$, which has virtually the same pK_a .

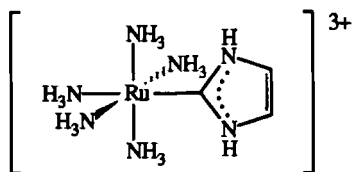
The decrease in pK_a values observed on coordination of azoles and azines to transition metals (Table I) is indicative of σ -electron donation from ligand to metal being the dominant interaction, with metal-to-ligand backbonding effects being minimal. However, a remarkable effect is observed among the group 8 metals, where coordination to the L_5M^{2+} moiety *increases* the pK_a of the coordinated ligand, most notably in the Os(II) complex $[\text{Os}(\text{NH}_3)_5\text{pzH}]^{3+}$ (**24**) where the ligand pK_a is raised nearly 7 pK_a units on coordination. This has been ascribed to $d\text{-}\pi^*$ backbonding from the filled metal d -orbitals to the unoccupied π^* orbitals of the ring. This effect becomes larger going down the group as the metal orbitals increase in both size and energy, allowing more efficient overlap with the ligand orbitals.



(24)

Metal coordination of 4-substituted imidazoles removes the possibility of tautomerism in the same way as does N-alkylation, thus rendering C-4 and C-5 chemically inequivalent. This then allows comparison of the acidities of the 4- and 5-substituted isomers. Thus the $[\text{Co}(\text{NH}_3)_5\text{4-MeimH}]^{3+}$ ion (**4**) is found to be slightly (0.24 pK_a units) less acidic than its 5-substituted isomer (**3**), reflecting the proximity of the electron-donating methyl substituent to the site of deprotonation in the former complex (84IC1851). A more pronounced difference in acidity between the 4- and 5-substituted isomers is observed in the $\text{Co}(\text{NH}_3)_5^{3+}$ complexes of 4(5)-bromoimidazole, where the 5-bromo isomer (**5**) is now significantly (~ 1.7 pK_a units) less acidic than the 4-bromo complex (**6**), in which inductive electron withdrawal by the bromine substituent reduces electron density at the adjacent nitrogen atom [91JCS(D)3031].

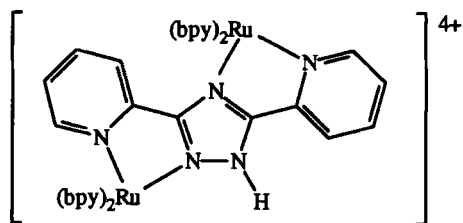
The pK_a of the unusual C-bound imidazole complex $[\text{Ru}(\text{NH}_3)_5\text{imH}_2]^{3+}$ (**25**) (11.0) is of note, as, in this species, the ligand is formally the neutral C-2 deprotonated ylide, which is stabilized via metal coordination. In this case, comparison should be made with the pK_a of *protonated* imidazole (7.0) and the observed value is in agreement with the poorer electron-



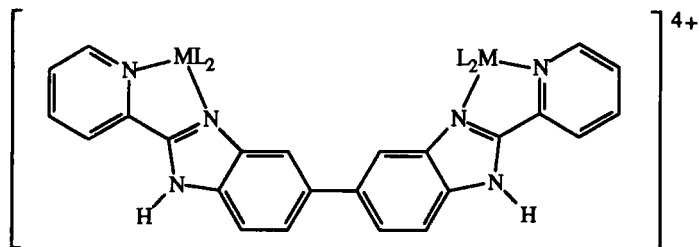
(25)

withdrawing effect of the $\text{Ru}(\text{NH}_3)_5^{3+}$ group compared to a proton (82IC3361).

Reedijk and co-workers have prepared and studied a variety of Ru(II) complexes of pyridyl- and pyrazinyl-substituted 1,2,4-triazoles of which **26** is an example. In all cases the heterocyclic ligands were chelated to the metal center via one azole and one azine nitrogen atom and, in addition to various electrochemical and spectroscopic studies, pK_a values for the "pyrrole" proton of the triazole ring were obtained. The $\text{Ru}(\text{bpy})_2^{2+}$ com-



(26)



(27) $\text{M} = \text{Ru}$, $\text{L} = \text{bpy}$

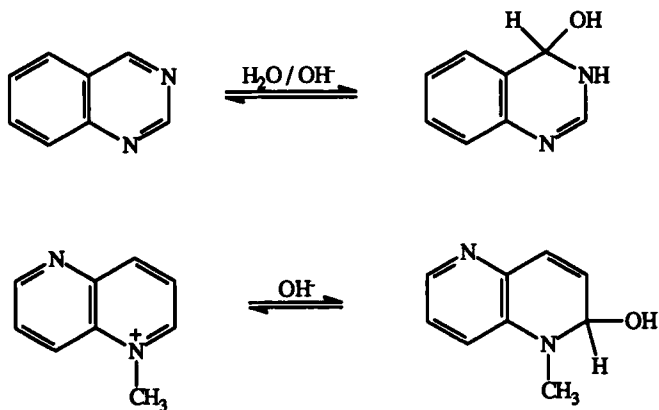
(28) $\text{M} = \text{Ru}$, $\text{L} = \text{phen}$

(29) $\text{M} = \text{Os}$, $\text{L} = \text{bpy}$

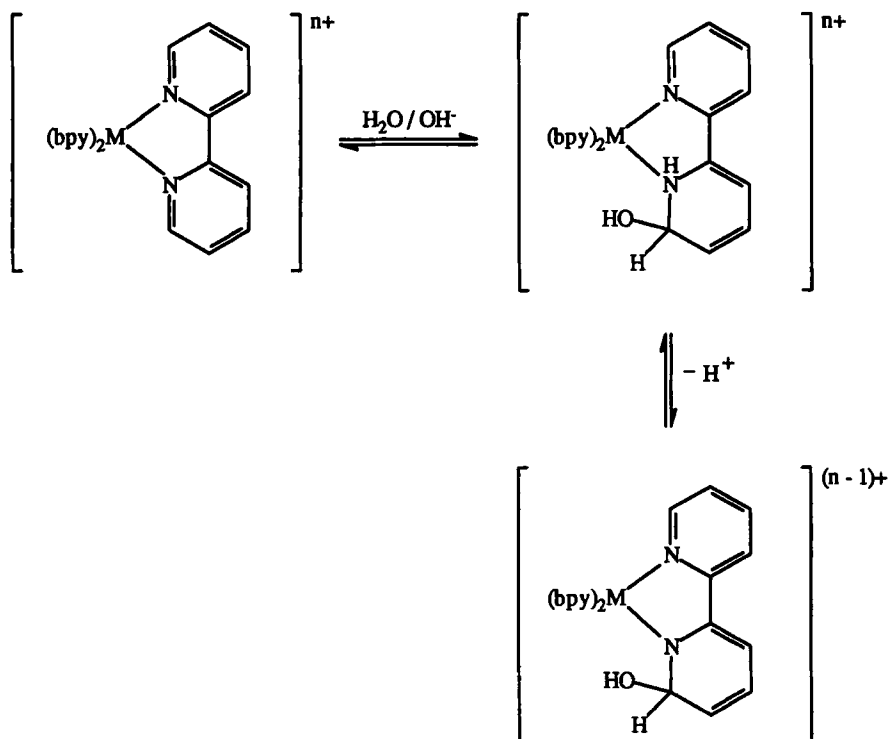
plexes were found to be stronger acids than the free ligands by approximately 4 pK_a units. Such values show that $d-\pi^*$ backbonding in these complexes is outweighed by σ -donation from ligand to metal [88IC2185; 90JCS(D)2425; 91IC3263]. The acidities of a series of binuclear complexes $[\text{M}(\text{L})_2(\text{bpbimH}_2)\text{M}(\text{L})_2]^{n+}$ ($\text{M} = \text{Ru}, \text{Os}$; $\text{L} = \text{bpy}, \text{phen}$; $\text{bpbimH}_2 = 2,2\text{-bis}(2\text{-pyridyl})\text{bibenzimidazole}$; $n = 4, 5, 6$) (**27–29**) have been studied to investigate the nature of the mixed-valence complexes. The $\text{M}(\text{II})\text{--M}(\text{II})$ complexes were found to have higher pK_a values than the free ligand, consistent with substantial $d-\pi^*$ backbonding, whereas the absence of such interactions in the $\text{M}(\text{III})\text{--M}(\text{III})$ species was demonstrated by their lower pK_a values, indicating the metal ions in this case are acting solely as Lewis acids. Of greatest interest in these systems were data for the mixed-valence $\text{M}(\text{II})\text{--M}(\text{III})$ complexes, where the pK_a values would be a sensitive probe of the structures of these ions. In all cases it was found that the two pK_a values of these mixed-valence complexes were very similar to those of the individual $\text{M}(\text{II})$ and $\text{M}(\text{III})$ components, providing good evidence that these species have a localized "valence-trapped" structure (91IC3843).

IV. Covalent Hydration and Pseudobase Formation

$\text{C}=\text{N}$ imine bonds of certain nitrogen heterocycles have long been known to undergo hydration in aqueous solution through addition of water across the double bond to give species termed "covalent hydrates." This process is well documented and several reviews are available [65AHC(4)1, 65AHC(4)43; 76AHC(20)117]. Similarly, the nucleophilic addition of hydroxide ion to N -alkyl heterocyclic cations gives the neutral "pseudobase" compounds (Scheme 6) [79AHC(25)1]. Both processes apparently require the heterocyclic ring to be electron deficient and usually involve species containing more than one heteroatom and/or strongly electron-withdrawing substituents, which facilitates nucleophilic attack at a ring carbon. In order to explain the apparently anomalous behavior of a number of bis- and tris-diimine (diimine = bpy , phen , terpy) metal complexes on treatment with base, Gillard has proposed that σ -coordination of a heterocycle to a metal ion via the heteroatom results in activation of the ligand to covalent hydration and pseudobase formation due to the Lewis acidity of the metal ion (Scheme 7) (73CC585; 74MI1). This hypothesis has been the subject of considerable controversy and numerous alternative interpretations of Gillard's experimental data have been advanced. The literature pertaining to this subject has been well reviewed [75CCR(16)67; 83CCR(50)209, 83MI1] and the purpose of this section is to discuss the relevant recent literature.



SCHEME 6



SCHEME 7

The possibility of covalent hydration in metal–heterocycle complexes was initially suggested in 1969 by Gillard and Heaton to explain their failure to resolve a number of enantiomeric *cis*-[M(N-N)₂X₂]⁺ complexes (M = Rh, Ir; N-N = bpy, phen; X = Cl, Br) [69JCS(A)451]. A subsequent study of the aqueous chemistry of [Pt(bpy)₂]²⁺ showed changes in the electronic spectrum of this ion on addition of base that were fully reversible on reacidification. In addition, the ¹H NMR signal (100 MHz) assigned to the 6,6' protons was lowered in intensity on addition of base. These observations were interpreted by Gillard in terms of reversible nucleophilic attack by OH⁻ at the 6-position of the bipyridine ring (73CC585), although Nord and co-workers proposed that the data were also consistent with simple addition of OH⁻ to the metal center to form a five-coordinate complex [75ACS(A)270]. Results obtained from a subsequent investigation of the ¹H and ¹³C NMR spectra of [Pt(bpy)₂]²⁺ at 270 MHz supported the latter interpretation (79JA6118). Several recent studies have addressed the question of covalent hydration and pseudobase formation in metal–heterocycle complexes. Treatment of an aqueous solution of [Cr(bpy)₃]³⁺ with OH⁻ was found to result in luminescence quenching that was reversible on addition of acid, although the electronic spectrum of this ion showed no pH dependence. This quenching was suggested to be due to chemical reaction of the complex with OH⁻ at the ligand rather than formation of a seven-coordinate species via OH⁻ attack at the metal, although the reasoning behind this choice of mechanism was not stated (89MI5). The reaction of a series of [M(5-NO₂phen)Cl₂] complexes (M = Ni, Co, Cu, Pt, Pd) with aliphatic amines in DMSO or DMF was found to give immediate color changes that were reversible on addition of acid. The rate of reaction of the Pt and Pd complexes with propylamine was found to be similar, arguing against reaction at the metal center. The spectral changes were thus ascribed to nucleophilic attack of the amine at the ligand to form Meisenheimer-type adducts (84MI6). Seddon and co-workers have refuted claims of covalent hydration in the complexes *trans*-[Pt(py)₄Cl₂]²⁺ and *cis*-[Ru(bpy)₂(py)₂]²⁺. The acidic solution obtained on dissolution of the former complex in water, originally used as evidence of covalent hydration (81CC448), was shown to be due to the presence of an acidic impurity; NMR studies of the pure compound showed no evidence for nucleophilic attack at the ligand [87JCS(D)293]. A 2-D ¹H NMR (360MHz) study of the ruthenium complex in *d*⁶-DMSO gave no evidence for hydration on addition of base [88JCS(D)1837] in contrast to a previous study (100 MHz) in which the H-6 proton resonance of the bipyridine ligand was apparently observed to move significantly on addition of base (77CC776). No variation in the ¹³C spectrum of the complex was observed with pH. Ghosh *et al.* have proposed a mechanism for

the reduction of the $[M(bpy)_3]^{3+}$ ions ($M = Fe, Ru, Os$) by water that involves rate-determining covalent hydration of the bipyridine ligand (84JA4772). However, Lay has pointed out that the products of such reactions are ligand N-oxide species, the formation of which would be unlikely from covalent hydrates. He has proposed an alternative mechanism involving water or OH^- attack at the metal center to form a seven-coordinate intermediate to be more likely in view of the propensity of $Ru(III)$ species to undergo associative ligand-exchange reactions (85IC4707).

Lay has questioned the validity of Gillard's assertion that coordination of a metal ion can be considered analogous to quaternization with respect to activation of the heterocyclic ring and has proposed that interactions between the ligand π -orbitals and the metal d -orbitals, which are absent in the N-alkylated systems, are important in determining the reactivity of the ligand (84IC4775). The polarization of the ligand on coordination to a metal ion is inherently weaker than that experienced on quaternization and $d-\pi^*$ backbonding from ligand to metal will offset the Lewis acid effect of the metal to some extent, leading to little or no activation of the ligand. On the basis of metal-ligand π interactions he has argued qualitatively that activation of metal-coordinated heterocycles toward nucleophilic attack should be greatest for the poor π -donors $Fe(III)$, $Ru(III)$, and $Cr(III)$. However, these metal ions are also found to be very efficient at activating the ligands toward other reactions such as deprotonation and are themselves susceptible to direct nucleophilic attack at the metal to give the 7-coordinate species that have been advanced to explain the anomalous behavior of a number of complexes. Constable, although substantially agreeing with the above points has argued that, whereas coordination may not significantly alter the *total* electron density of the ligand, it will certainly influence the distribution of this electron density between the σ - and π -systems, with ligand orbitals of π -symmetry being most affected (86MI2). In an attempt to quantify the discussion, Clack and Gillard have carried out INDO calculations on pyridine, *N*-methyl pyridinium ion, and a number of $Fe(III)$ -pyridine and $Co(III)$ -pyridine complexes. The results of these studies did indeed show a net flow of electron density out of the ring on both quaternization with Me^+ and coordination to the metal ion and, in all cases, C-2 of the pyridine ring was found to be deficient in both π and σ electrons, giving a net positive charge at this site (88MI1). However, these results cannot be used as evidence for pseudobase formation in these complexes, as the *N*-methylpyridinium cation, which is calculated to have a comparable positive charge at C-2, is known not to form a pseudobase [79AHC(25)1].

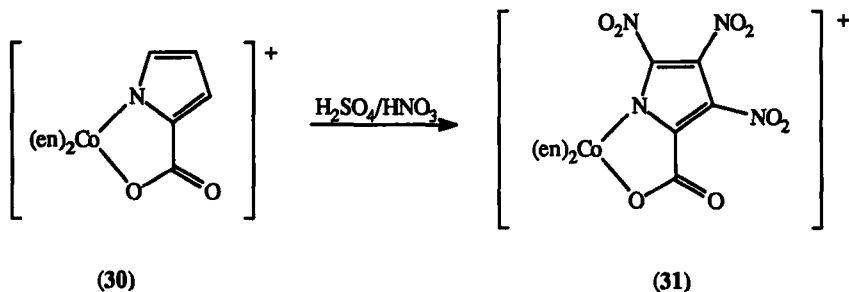
Although there are cases where coordination of a heterocycle to a metal ion undoubtedly activates the ligand toward nucleophilic attack (84MI5), there are still, as has been previously stated, "no proven examples of complexes of 2,2'-bipyridine, 1,10-phenanthroline or pyridine forming covalent hydrates" [87JCS(D)293].

V. Reactions of Coordinated Heterocycles

A. FIVE-MEMBERED RINGS

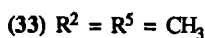
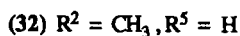
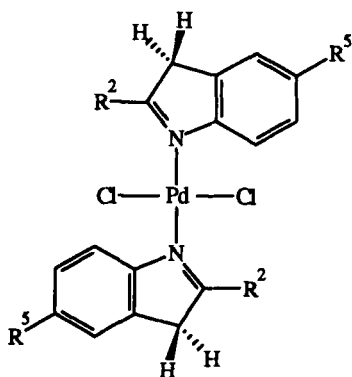
1. Pyrroles and Indoles

The nitrogen atom of pyrrole and its derivatives is feebly basic due to the involvement of the lone pair of electrons in the aromatic π system, and thus examples of neutral pyrroles bound to transition metals via the heteroatom are rare (except of course in the tetrapyrrolic metalloporphyrin systems, where electron delocalization substantially alters the electron-donor properties of the heterocycle). Sargeson and co-workers have studied the reactivity of pyrrole-2-carboxylic acid chelated to $\text{Co}(\text{en})_2^{3+}$. This complex was prepared in two ways: direct reaction of the ligand with $[\text{Co}(\text{en})_2(\text{OH})(\text{H}_2\text{O})]^{2+}$ and oxidation of the $\text{Co}(\text{III})$ -coordinated 5-hydroxypyrrolidine-2-carboxylic acid precursor with SOCl_2 . The product (30) was found to be chelated via the carboxylate oxygen and the pyrrole nitrogen, necessitating deprotonation at these sites. The H-3 and H-4 aromatic protons of the pyrrole ring in this complex were found to exchange rapidly at pH 0–1, whereas under the same conditions the free ligand shows little reaction, indicating that coordination to $\text{Co}(\text{III})$ activates the ligand toward electrophilic attack. More remarkable is the facile nitration of the coordinated ligand in $\text{H}_2\text{SO}_4/\text{HNO}_3$ at room temperature

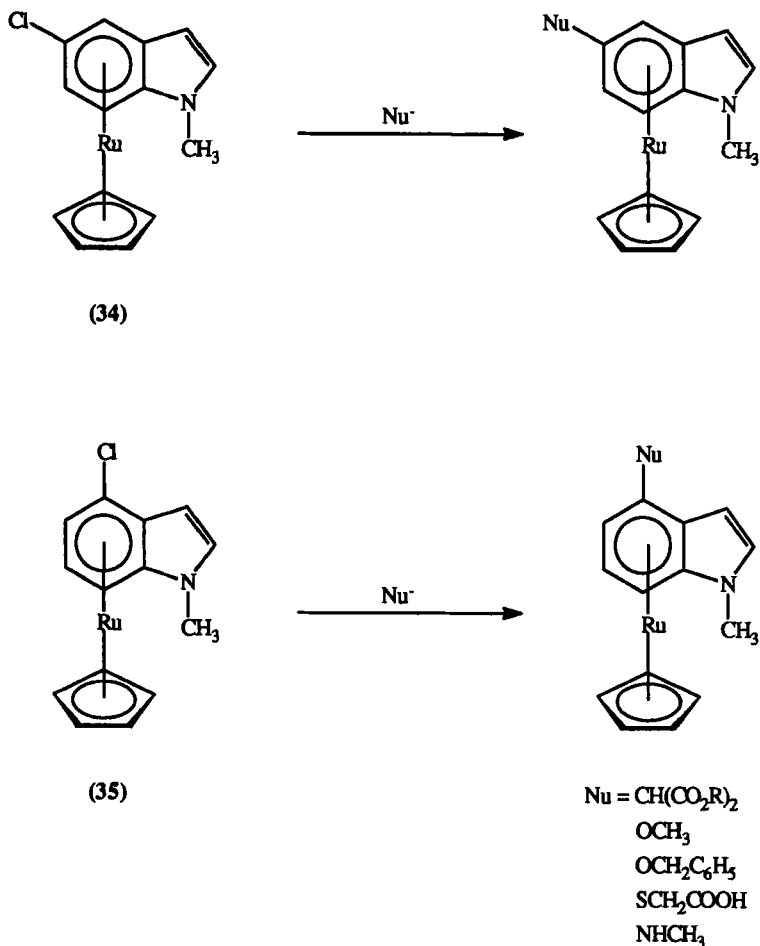


SCHEME 8

to give the trinitropyrrole (**31**) (Scheme 8) [91JCS(D)621] as attempted nitration of free pyrroles under such strongly acidic conditions gives only intractable tars (84MI1). Indoles having strongly electron-donating substituents at C-2 are known to undergo tautomerism to the *3H* indolenine form, thus leaving the nitrogen atom free to coordinate to a metal ion. This has been observed in the complexes [Pd(2-methylindole)Cl₂] (**32**) and [Pd(2,5-dimethylindole)Cl₂] (**33**) where crystal structural and NMR

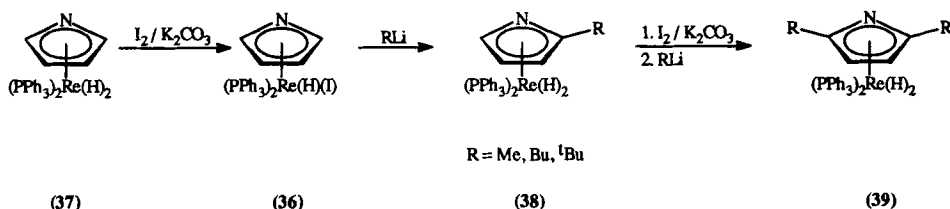


evidence showed coordination of the neutral ligand in the *3H* form. Metal–ligand binding in these complexes was weak and the indole ligands were readily displaced by both pyridine and DMSO, thus preventing studies of ligand reactivity (90IC1856). However, some π -bound indoles are sufficiently robust to allow such reactions to be investigated and it has been found that facile nucleophilic displacement of electron-withdrawing aromatic substituents can occur in these systems. Thus complexes of the type [Ru($\eta^5\text{-C}_5\text{H}_5$)(η^6 -chloroindole)]⁺ (**34,35**) were found to react with a range of carbon, oxygen, nitrogen, and sulfur nucleophiles to give substitution of the chlorine atom in excellent yields (Scheme 9) (87CC1493; 88MI4). The same authors also found that the analogous nitroindoles reacted similarly to give nucleophilic displacement of the nitro group (88CC1621). The reactivity of these complexes has recently been reviewed [91JOM(417)313]. Regioselective nucleophilic alkylation of the π -bound pyrrole ring has been observed in the rhenium hydride complex [Re(PPh₃)₂($\eta^6\text{-C}_5\text{H}_4\text{N}$)(H)(I)] (**36**), which was prepared from the dihydrido complex [Re(PPh₃)₂($\eta^6\text{-C}_5\text{H}_4\text{N}$)(H)₂] (**37**) by reaction with I₂/K₂CO₃ in di-



SCHEME 9

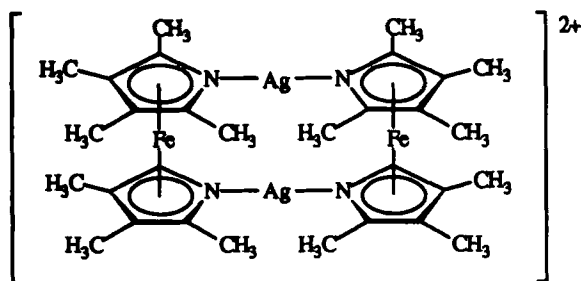
chloromethane at room temperature. Reaction of the iodo compound with one equivalent of RLi ($\text{R} = \text{Me}$, $n\text{-Bu}$, $t\text{-Bu}$) gave high yields of the 2-alkylated pyrrole complex (**38**) with migration of the displaced proton to the metal center and loss of iodide. Treatment of this complex with $\text{I}_2/\text{K}_2\text{CO}_3$ and addition of further RLi gave the 2,5-disubstituted product (**39**). The dihydrido complex (**37**) was also found to undergo electrophilic reactions with methyltriflate and acyl chlorides at the deprotonated nitrogen atom to give the N-substituted pyrrole [85JA3374; 87JOM(326)C17, 87JOM(333)71]. A later study found **37** to react directly with BuLi to give ring-deprotonation and lithiation exclusively at the 2-position and



SCHEME 10

subsequent treatment with methyl iodide gave the 2-methyl complex in excellent yield [89JOM(362)C31].

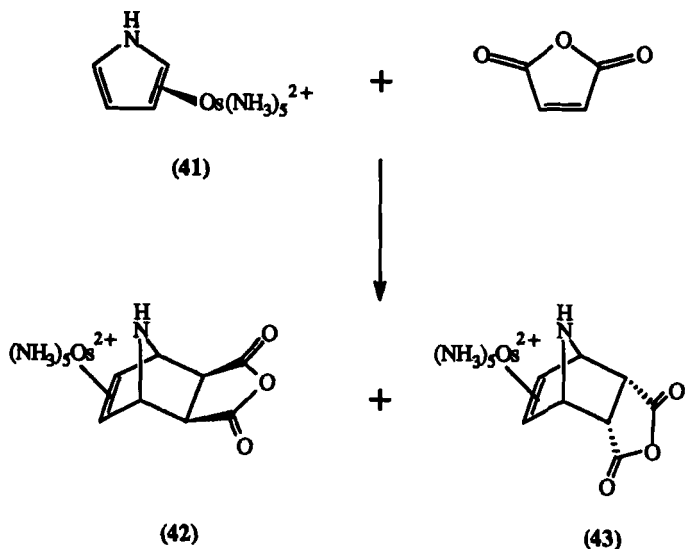
Reactions at the deprotonated ring nitrogen atom of π -coordinated pyrrole have been observed in azaferrocene and diazaferrocene complexes. These are prepared by treatment of the neutral pyrrole complexes with strong base, and the basicity of the ring nitrogens (pK_a 7.2) allows facile reaction with a variety of Lewis acids. Thus $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\eta^5\text{-C}_4\text{Me}_4\text{N})]$ (the conjugate base of **20**) reacted with CH_3I , B_2H_6 , CH_3COCl , and $\text{Fe}_2(\text{CO})_9$ to give the corresponding N- CH_3 , N- BH_3 , N-COCH $_3$, and N- $\text{Fe}(\text{CO})_4$ derivatives, respectively (89CB1891). Similarly, octamethyl-diazaferrocene $[\text{Fe}(\eta^5\text{-C}_4\text{Me}_4\text{N})_2]$ was found to undergo metal-coordination at the nitrogen atoms on reaction with AgBF_4 to give the novel silver-bridged dimeric species (**40**) (89CB2275). Octamethyl-diazaferrocene also reacted with Lewis acids at the deprotonated nitrogen in the same way as the monopyrrole complex, and in addition, reaction with succinyl chloride gave reaction at both nitrogen atoms to give a novel ring-linked species (91CB997).



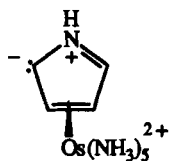
(40)

The synthesis of η^2 -bound pyrrole complexes has recently been reported and studies have shown remarkable differences between the reactivity of

the coordinated and free ligand. Pyrrole, thiophene, and furan differ in their Diels–Alder reactivity, the latter being extremely reactive toward dienophiles, whereas pyrrole does not react in the absence of a catalyst. In contrast, the η^2 -bound complexes of these ligands $[\text{Os}(\text{NH}_3)_5\text{L}]^{2+}$ showed a reversal of this trend, with the thiophene and furan complexes failing to react with excess maleic anhydride at room temperature. The pyrrole complex (**41**) was found to react completely within 5 min under the same conditions to give both the *exo* (**42**) and *endo* (**43**) cycloadducts, with the metal ion bound *exo* in both cases (Scheme 11). The *N*-methylpyrrole complex was found to react even faster, thus ruling out an *N*-bound species as an intermediate (89JA5969) and the reaction mechanism was postulated to involve the ylide (**44**). Further studies of the pyrrole complexes have shown that coordination of the ligand in an η^2 -fashion transforms it into an enamine; the crystal structure of $[\text{Os}(\text{NH}_3)_5(2,3\text{-}\eta^2\text{-2,5-dimethylpyrrole})]$ shows C-2 to approximate sp^3 geometry, with concomitant shortening of the C3—C4 bond and lengthening of the C4—C5 bond relative to the free pyrrole. This complex reacted with triflic acid to give protonation at C-4 exclusively, in contrast to free pyrrole, which reacts at the α -position. Remarkably, protonation at C-4 was also observed on treatment of the complex with the weakly acidic anilinium ion. Reaction of the protonated complex with an amine base regenerated the starting

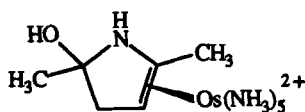


SCHEME 11



(44)

material (91JA6682) and pK_a values for this process have been measured for a number of pyrroles (Scheme 5) (see Section III). Although the pyrrole and *N*-methylpyrrole complexes show essentially the same ^1H NMR spectra in d^6 -acetone and D_2O , the spectrum of the 2,5-dimethyl complex in D_2O gave evidence for conversion ($\sim 90\%$) of the ligand to its hydrate (45)



(45)

through addition of water across the C4—C5 bond. The 5-ethylpyrrole complex behaved similarly ($\sim 45\%$ hydration) but the 1,2,5-trimethyl species decomposed under the same conditions. The hydrated 2,5-dimethyl complex could be dehydrated by treatment with NaBPh_4 . ^1H NMR spectra were consistent with stereospecific D^+ addition at C-4 from the face of the ring *anti* to the metal for both the hydration and the protonation processes (92JA5684).

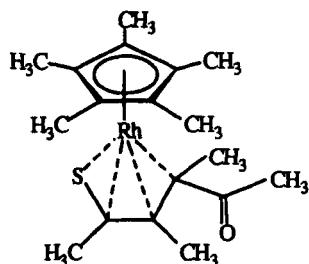
2. Thiophenes

Catalytic hydrodesulfurization (HDS) is a very important industrial process that involves removal of sulfur from crude oils by high-temperature ($\sim 400^\circ\text{C}$) treatment with hydrogen over Co- or Ni-promoted Mo or W catalysts supported on alumina. In an attempt to determine the mechanism of this process, many transition metal complexes of thiophene, a sulfur-containing heterocycle that is particularly difficult to desulfurize, have been prepared and their reactivities studied in order to compare their behavior with those of the free thiophenes that give H_2S and C_4 hydrocarbons under HDS conditions (88ACR387). Thiophene can conceivably bind to the catalyst surface by either σ -donation via a sulfur electron pair or through a variety of π -coordination modes involving the aromatic system

of the ring. Both σ - and π -complexed thiophenes have been observed in model compounds and studies have shown that π -coordination is considerably stronger than σ and in many cases activates the bound thiophene toward nucleophilic addition and ring-cleavage reactions under mild conditions.

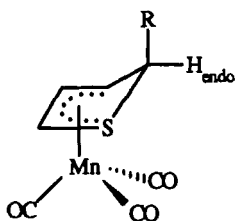
Deuterium exchange in free thiophene occurs only under highly basic conditions (84MI4). In contrast, it has been found that, under HDS conditions, thiophene undergoes deuterium exchange with D_2 primarily at the C-2 and C-5 (α) positions, with very little incorporation seen at C-3 and C-4. This was initially used as evidence that thiophene binds to the catalyst surface via the S-atom, thus activating the adjacent positions of the ring. However, base-catalyzed proton exchange at the 2- and 5-positions under mild conditions has been observed in the π -bound complex $[Ru(\eta^5\text{-thiophene})(\eta^5\text{-C}_5\text{H}_5)]^+$ (**14**) (85JA5569). No evidence for exchange at the 3- and 4-positions was obtained in this study, although a subsequent investigation of the rates of deuterium exchange in complexes of this type gave nonzero rate constants for reaction at these sites (87MI5). This study investigated the kinetics of base-catalyzed deuterium exchange in a number of $[Ru(\eta^5\text{-L})(\eta^5\text{-C}_5\text{H}_5)]^+$ complexes (L = thiophene, 2-methylthiophene, 3-methylthiophene, 2,5-dimethylthiophene) at 23°C and the data obtained supported a second-order rate law involving both the ruthenium complex and the hydroxide ion. The rates of exchange at the 2- and 5-positions were found to be much greater (3–5 orders of magnitude) than at either the 3- and 4-positions or the methyl groups. The 2,5-dimethylthiophene complex, in which the α -positions are blocked, gave exchange at the 3- and 4-positions. The data were interpreted in terms of rate-determining proton abstraction from the thiophene by OH^- and subsequent deuteration by solvent (CD_3OD). Similar enhanced reactivity of positions adjacent to the sulfur atom has been observed in $[Cr(CO)_3(\text{thiophene})]$, where treatment with excess BuLi gives the 2,5-dilithio derivative exclusively [83JOM(244)C21] whereas the analogous benzo[*b*]thiophene complex gave initial lithiation at C-2 [87JOM(336)C44]. Although no H/D exchange was observed in free tetramethylthiophene (TMT) at 150°C in D_2O , the complexes $[Ru(TMT)(H_2O)_3]^{2+}$ and $[Ru(TMT)_2]^{2+}$ were found to undergo selective deuteration at the 2- and 5-methyl groups under the same conditions (91MI1). On treatment with aqueous OH^- , the complex $[Rh(\eta^5\text{-TMT})(\eta^5\text{-C}_5\text{Me}_5)]^{2+}$ gave the ring-opened species $[Rh(\eta^4\text{-MeCOC}_3\text{Me}_3\text{S})(\eta^5\text{-C}_5\text{Me}_5)]$ (**46**) in contrast to the behavior of the normally hydrolysis-inert free thiophenes (90MI4).

An important step in the HDS process is postulated to be loss of aromaticity of the thiophene ligand. η^5 -coordination of thiophene in $[Mn(CO)_3(\eta^5\text{-thiophene})]^+$ has been found to activate the 2-position of the ring to



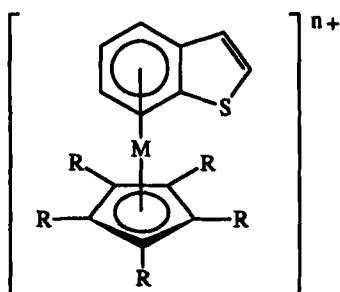
(46)

nucleophilic attack by H^- , CN^- , and PBU_3 , thereby disrupting the π -system and giving products in which the thiophene ring is now η^4 -bound to the metal ion and is no longer planar (47–49). Protonation of the hydride- or cyanide-addition product with HCl gave uncharacterized complexes that yielded the 2,3-dihydrothiophene on dissolution in MeCN (84JA2901). The stereochemistry of the hydride addition process leading to 47 has

(47) $\text{R} = \text{H}$ (48) $\text{R} = \text{CN}$ (49) $\text{R} = \text{PBU}_3$

been investigated using deuterium labeling and it was found that both *exo*- and *endo*-deuterated products were obtained, with the *exo* isomer predominating (78 : 22 *exo:endo*). Abstraction of the *exo* hydride only was observed on treatment with Ph_3C^+ (87MI4). The group 9 complexes $[\text{M}(\eta^5\text{-thiophene})(\eta^5\text{-C}_5\text{Me}_5)]^{2+}$ ($\text{M} = \text{Rh}, \text{Ir}$) were found to be similarly activated toward nucleophilic attack by a variety of phosphines at the 2-position to give η^4 -bound species. However, attempted hydride addition to the 2-position of the iridium complex using NaBEt_3H instead resulted in a two-electron reduction of the metal ion (88MI5). This study also investigated reactions of a number of benzo[*b*]thiophenes π -bound to $[\text{Ru}(\eta^5\text{-C}_5\text{H}_5)]^+$

(50) and $[\text{Ir}(\eta^5\text{-C}_5\text{Me}_5)]^{2+}$ (51) with various nucleophiles (H^- , MeO^- , $(\text{MeO}_2\text{C})_2\text{CH}^-$, EtS^- , PR_3). The fused heterocycles are η^6 -bound to the metal ion via the π system of the benzene ring and nucleophilic attack occurred solely at the four available carbon sites of this ring to give a mixture of the corresponding cyclohexadiene isomers with reaction at C-7 being favored in all cases. In contrast to the manganese complex discussed above, hydride (deuteride) addition was found to occur only at the *exo* face of the benzothiophene ligand.

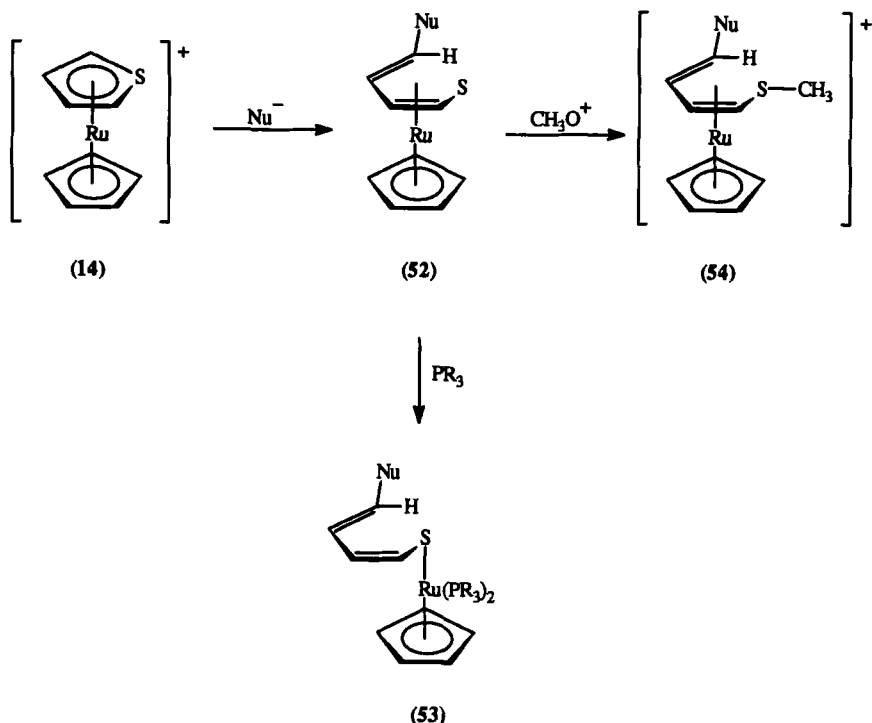


(50) $\text{R} = \text{H}$, $\text{M} = \text{Ru}$, $n = 1$

(51) $\text{R} = \text{CH}_3$, $\text{M} = \text{Ir}$, $n = 2$

Reaction of $[\text{Ru}(\eta^5\text{-L})(\eta^5\text{-C}_5\text{H}_5)]^+$ ($\text{L} = \text{thiophene}$, 2-methylthiophene) with nucleophiles (MeO^- , MeS^- , EtS^- , PrS^- , $(\text{MeO}_2\text{C})_2\text{CH}^-$) resulted in initial cleavage of the C—S bond of the thiophene ligand and formation of an η^5 -bound butadienethiolate (52). These species were found to undergo subsequent reactions, either with PR_3 , which displaced the alkenes from the coordination sphere of the metal giving the η^1 sulfur-bound complex (53) (87MI6), or with Me_3O^+ , to give methylation of the sulfur atom and formation of the thioether (54) (Scheme 12) [88JOM(355)359]. The corresponding 2,5-dimethylthiophene complex showed no reaction with the above nucleophiles, but did however react with hydride (LiAlH_4 , NaBHET_3) to give the ring-opened butadienethiolate complex analogous to 53, which was characterized by a crystal structure [87AG(E)909].

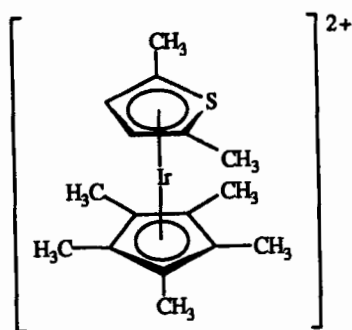
Two-electron reduction of the 18-electron $[\text{M}(\eta^5\text{-L})(\eta^5\text{-C}_5\text{Me}_5)]^{2+}$ ($\text{M} = \text{Ir}$, $\text{L} = 2,5\text{-dimethylthiophene}$ (55); $\text{M} = \text{Rh}$, $\text{L} = 2,3,4,5\text{-tetramethylthiophene}$) complexes gives the corresponding η^4 -bound thiophene species in which the ligand has lost its aromaticity and now acts as a 4-electron donor via the diene as shown in Scheme 13 for the Ir complex. This was first demonstrated in the crystal structure of $[\text{Ir}(\eta^4\text{-2,5-dimethylthiophene})(\eta^5\text{-C}_5\text{Me}_5)]$ (56), where the thiophene ring was found to be nonplanar with the sulfur atom lying 0.905 Å out of the plane of the



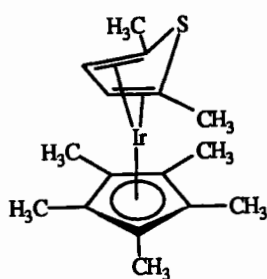
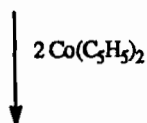
SCHEME 12

four carbon atoms (89M12). The sulfur atom is found to be unusually nucleophilic, as it now no longer contributes an electron pair to the aromatic system and undergoes reactions more typical of sulfides. Thus the iridium complex reacted with both $\text{Me}_2\text{S}\cdot\text{BH}_3$ and $\text{THF}\cdot\text{BH}_3$ to give the BH_3 adduct (57) in which η^4 -coordination was again confirmed by a crystal structure (90JA199). Likewise, reaction with R_3O^+ ($\text{R} = \text{Me}, \text{Et}$) gave the S-alkylated thiophene (90MI3). The dimethylthiophene complex (55) was also found to undergo a base-catalyzed isomerization to give a novel iridathiabenzene (58), oxidation of which regenerated 55.

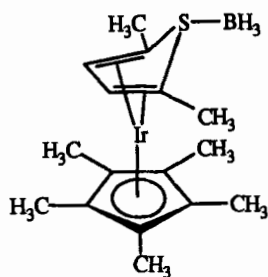
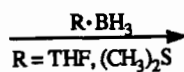
Stirring a toluene solution of the rhodium complex $[\text{Rh}(\eta^4\text{-2,3,4,5-tetramethylthiophene})(\eta^5\text{-C}_5\text{Me}_5)]$ (59) under oxygen resulted in extraordinarily facile oxidation at sulfur to give the S-oxide (60) in greater than 90% isolated yield (Scheme 14) (90JA2432). Thiophenes are ordinarily totally inert to oxygen and oxidation at sulfur is usually accomplished in low yield by reaction with mCPBA (84MI3). The η^4 -rhodium complex (59) also reacted with $\text{Fe}(\text{CO})_5$ to give a heterobimetallic complex in which the $\text{Fe}(\text{CO})_4$ moiety is coordinated to the sulfur atom. Thermolysis of this at



(55)

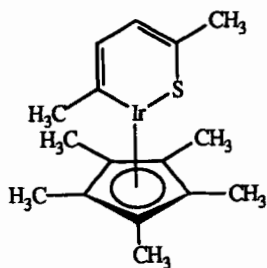


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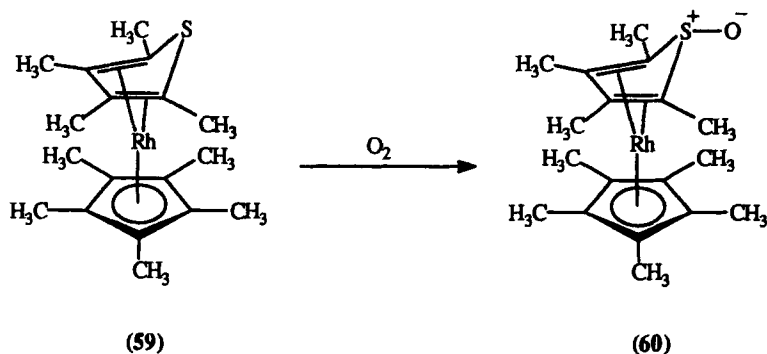


(57)

SCHEME 13



(58)

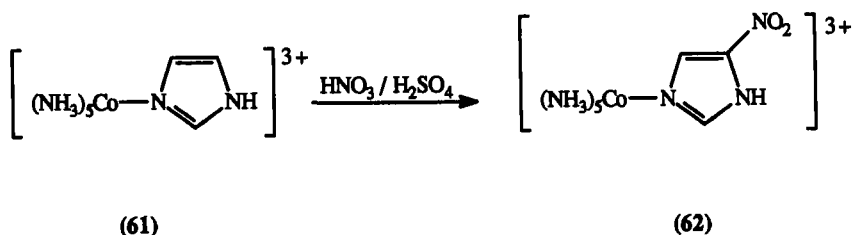


SCHEME 14

110°C resulted in extrusion of sulfur and formation of an iron metallacycle (91MI3). Loss of sulfur from the thiophene ring has also been observed on reaction of the η^4 complex $[\text{Rh}(\eta^5\text{-C}_5\text{Me}_5)(\eta^4\text{-thiophene})]$ with $\text{Fe}_3(\text{CO})_{12}$ at 110°C (89MI3), and upon flash vacuum pyrolysis of the η^4 -2,5-dimethylthiophene 1,1-dioxide complex $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)(\eta^4\text{-C}_6\text{H}_8\text{SO}_2)]$ at 500–600°C, giving the coordinated dimethylcyclobutadiene (85MI1).

3. Imidazoles

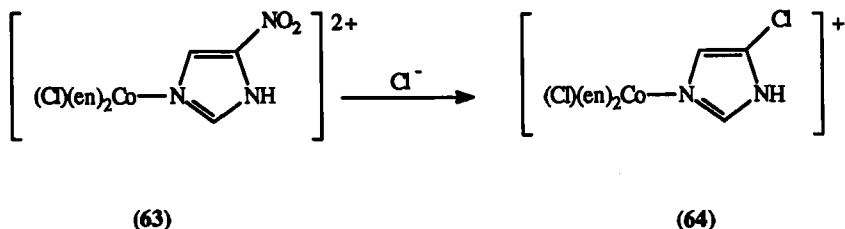
Metal complexes of imidazoles have been widely studied because of the importance of the histidine side chain as a metal binding site in biological systems and an extensive review of the chemistry of transition metal imidazole complexes is available (74CRV471). Most studies have concentrated solely on synthesis of these complexes, although in some cases reactivities of the coordinated ligands have been investigated. The effects of coordination to a transition metal on the acid/base properties of the pyrrolic nitrogen atom have already been discussed (see Section III) and in the absence of metal–ligand backbonding it is found that the Lewis-acidic metal ion acts as an electron acceptor, which should facilitate nucleophilic attack at the ligand. However, this aspect of the chemistry of coordinated imidazoles has been little investigated. Of greater interest has been the reaction of these species with electrophiles, where metal coordination prevents deactivating protonation at the pyridine-type nitrogen atom. Thus $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ (**61**) was found to undergo nitration at 0°C in $\text{H}_2\text{SO}_4/\text{HNO}_3$ in 97% yield to give the 4-nitro isomer (**62**) exclusively (Scheme 15), in stark contrast to free *N*-methylimidazole, which reacts in boiling $\text{H}_2\text{SO}_4/\text{HNO}_3$ to give a 29% total yield of the 4- and the 5-nitro isomers (83IC678). No nitration of $[\text{Co}(\text{NH}_3)_5(4\text{-MeimH})]^{3+}$ (**4**) was



SCHEME 15

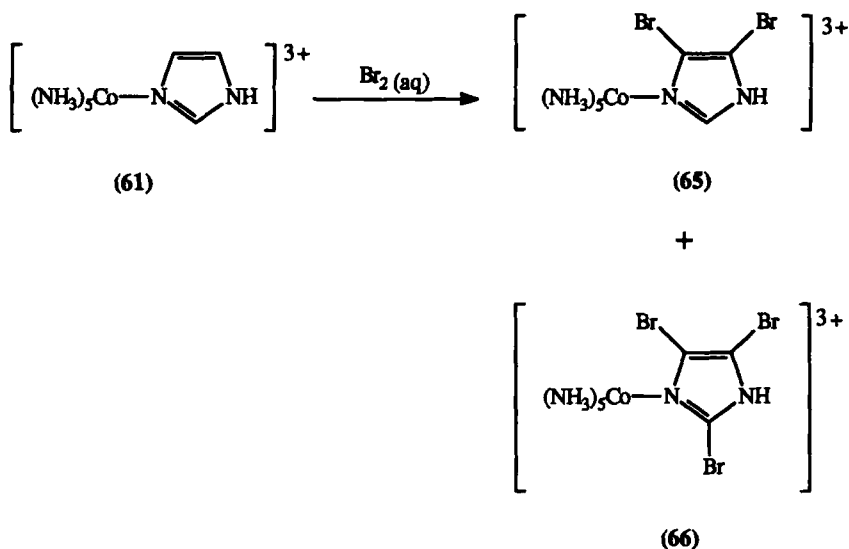
observed under forcing conditions, suggesting that even in the presence of an electron-donating ring substituent, reaction at C-2 or C-5 is prevented by the steric bulk of the $\text{Co}(\text{NH}_3)_5^{3+}$ moiety. The bis(ethylenediamine) complexes $\text{cis}[\text{Co}(\text{en})_2(\text{Cl})(\text{L})]^{2+}$ (L = imidazole, *N*-methylimidazole, histidine) were also found to nitrate at the 4-position of the ring, although in these cases the products were less robust than the analogous pentaammine complexes and dissociation of the nitrated imidazole ligands occurred readily (91IC4374). In contrast to the pentaammine complex, $[\text{Co}(\text{en})_2(\text{Cl})(4\text{-MeimH})]^{2+}$ was found to nitrate at the 5-position adjacent to the metal ion, presumably due to the different steric characteristics of the $\text{Co}(\text{en})_2\text{Cl}^{2+}$ moiety. Attempts to purify the mononitrated complex $[\text{Co}(\text{en})_2(\text{Cl})(4\text{-NO}_2\text{im})]^+$ (63) by column chromatography on Sephadex using aqueous NaCl as eluent resulted in nucleophilic displacement of the nitro group and formation of the 4-chloro derivative $[\text{Co}(\text{en})_2(\text{Cl})(4\text{-ClimH})]^+$ (64) (Scheme 16). Elution with NaClO_4 gave no such reaction and the 4-nitro complex was recovered unchanged. This is a rare example of metal-coordination activating the imidazole ring toward nucleophilic attack.

Imidazole is known to be very reactive toward halogens, both Br_2 and I_2 giving the 2,4,5-trihalo derivatives in aqueous solution, whereas treatment with Cl_2 appears to give uncharacterized ring-opened products (84MI2). Lambert and Jones, in a study of the kinetics of iodination of

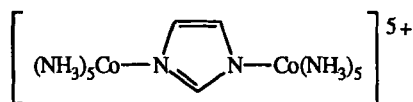


SCHEME 16

imidazole coordinated to Ni^{2+} , reported differences between the rate law for the complex and that for free imidazole (66JA5537). However, the presence of more than one nickel-imidazole species in solution ["98% of the imidazole is present as $\text{Ni}(\text{imH})^{2+}$ and the rest as higher complexes"] and the undoubted lability of these complexes must render the authors' conclusions uncertain. Buckingham and co-workers have carried out extensive studies of the bromination of imidazoles coordinated to $\text{Co}(\text{NH}_3)_5^{3+}$. Such complexes are better suited to kinetic studies owing to their inertness to ligand exchange and hydrolysis, and the diamagnetic d^6 low-spin configuration of the $\text{Co}(\text{III})$ ion allows use of NMR to identify products. In contrast to the free ligand where only tribromination is found, $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ (**61**) reacted rapidly with aqueous Br_2 to give a mixture of the 4,5-dibromoimidazole (**65**) and 2,4,5-tribromoimidazole (**66**) complexes (Scheme 17) (86AJC1465). Unlike the nitration of this complex, the $\text{Co}(\text{NH}_3)_5^{3+}$ group appears to provide no steric hindrance to substitution at the adjacent 5-position. Although no monobrominated complex could be isolated from the above bromination reaction, direct monobromination of coordinated imidazole at the 4(5) position was effected on treatment of the dimeric complex $[\text{Co}(\text{NH}_3)_5(\text{im})\text{Co}(\text{NH}_3)_5]^{5+}$ (**67**) with one equivalent of $\text{Br}_{2(\text{aq})}$ [91JCS(D)3031]. This study also investigated the reactions of various methyl-substituted imidazole complexes, the 4-Me and 5-Me iso-



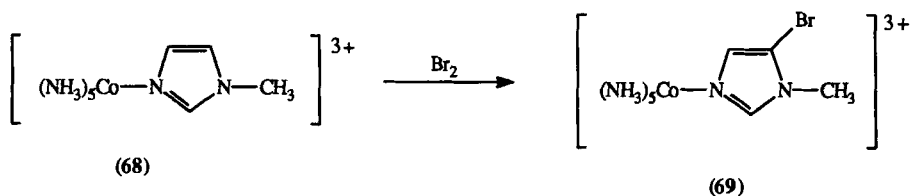
SCHEME 17



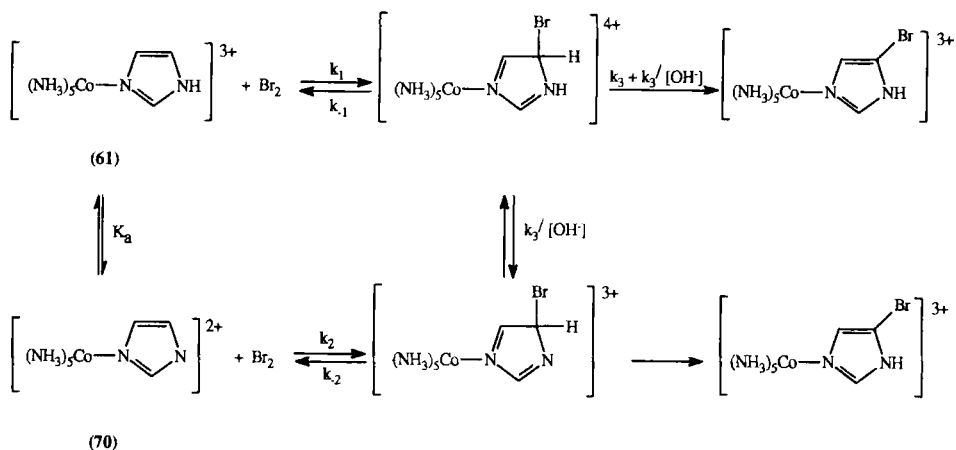
(67)

mers reacting with one equivalent of $\text{Br}_{2(\text{aq})}$ to give only monobromination at the adjacent carbon, whereas the 2-Me isomer under the same conditions gave the 4,5-dibromo derivative. Although all of these reactions were found to be relatively rapid (consumption of bromine was complete within 30 min) the same was not true of the *N*-methylimidazole complex (68), the bromination of which required reaction with excess $\text{Br}_{2(\text{t})}$ overnight to give the monobrominated complex $[\text{Co}(\text{NH}_3)_5(\text{N-Me}, 4\text{-BrimH})]^{3+}$ (69) (Scheme 18). This extraordinary difference between the reactivity of the free and coordinated ligand (the former undergoes facile tribromination) can be attributed to the inability of the *N*-methyl complex to deprotonate at nitrogen. Rate data for the bromination of a number of imidazole complexes gave complex pH and $[\text{Br}^-]$ dependences that were interpreted in terms of reaction of both the $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ (61) and the deprotonated $[\text{Co}(\text{NH}_3)_5(\text{im})]^{2+}$ (70) species with molecular bromine (Scheme 19) with rates for the latter being essentially diffusion controlled (91AJC981, 91JA2656). The observed polybromination of $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ can thus be rationalized; although the inductively electron-withdrawing bromine atom introduced (almost certainly at C-4) in the first bromination step will deactivate the ring toward further substitution, this effect is outweighed by the lowering of the pK_a of the complex, which produces a higher concentration of the extremely reactive conjugate-base form of the complex.

The reaction of $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ with $\text{Br}_{2(\text{aq})}$ in acetate or phosphate buffer gave, in addition to ring-brominated species, the imidazole-2,4,5-trione complex $[\text{Co}(\text{NH}_3)_5(\text{parabanate})]^{2+}$ (71). The same reaction also occurred on treatment of the imidazole complex with $\text{Cl}_{2(\text{aq})}$ in the absence

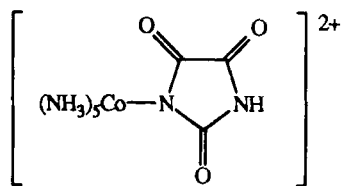


SCHEME 18

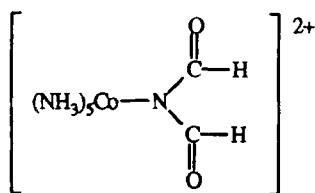


SCHEME 19

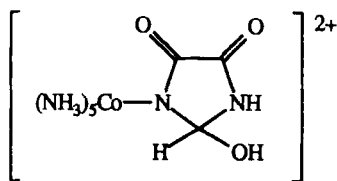
of buffer. $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ was also found to react with aqueous HOBr to give the ring-cleavage products $[\text{Co}(\text{NH}_3)_5(\text{N}(\text{CHO})_2)]^{2+}$ (72) and $[\text{Co}(\text{NH}_3)_5(2\text{-hydroxyimidazolidine-4,5-dione})]^{2+}$ (73). These ligands have not been previously identified as degradation products of imidazole (91IC1635).



(71)



(72)



(73)

Imidazoles are known to undergo exchange with solvent deuterium at C-2 and this has been proposed to occur via a mechanism involving OH^- attack on the imidazolium ion [65CI(L)1728; 70JOC1141]. Somewhat surprisingly then, no exchange is observed at the C-2 position of $[\text{Co}(\text{NH}_3)_5(\text{imH})]^{3+}$ (81MI1) although the N-methylated derivative $[\text{Co}(\text{NH}_3)_5(\text{N-Meim})]^{3+}$ (68) does deuterate at this position in basic solution (86UPI).

The Ru(III) complexes $(\text{imH}_2)_2[\text{Ru}(\text{imH})\text{Cl}_5]$ and *trans*-(imH_2) $[\text{Ru}(\text{L})_2\text{Cl}_4]$ (L = imidazole, 1-methylimidazole, 2-methylimidazole, 4-methylimidazole) have been shown to be promising antitumor agents of comparable activity to cisplatin. The mode of action of these complexes is unknown (87IC844, 87IC4366).

4. Pyrazoles

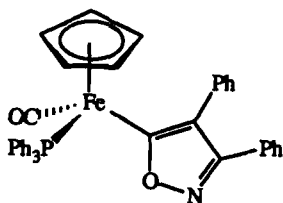
Rate data for the iodination of pyrazole in aqueous solution showed the reaction to be first-order in both iodine and heterocycle and an inverse first-order $[\text{H}^+]$ dependence was found over the pH range 5.96–6.74 (64JA2857). A kinetic study of the aqueous iodination of pyrazole coordinated to Ni^{2+} showed the coordinated ligand to react more rapidly, and a $[\text{H}^+]$ dependence that differed from that of the free ligand (82JA2460). However, the results of this study should be viewed with caution, as the presence of several nickel–pyrazole complexes in solution necessarily leads to uncertainties about the exact nature of the reactive species.

5. Isoxazoles

Isoxazole and its 3-unsubstituted derivatives are known to be base-sensitive, reacting with hydroxide ion to give ring-opening, whereas substituted isoxazoles are relatively resistant to nucleophilic attack [79AHC(25)147]. Both types of behavior are mirrored in metal complexes of these species. Thus the N-bound complex $[\text{Co}(\text{NH}_3)_5(\text{isoxazole})]^{3+}$ was found to undergo ring opening in aqueous NaOH to give (presumably) the coordinated cyanoenolate with a second-order rate constant of $467 \text{ M}^{-1} \text{ s}^{-1}$ (82IC2089). The C-bound isoxazole complex $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\text{CO})(\text{PPh}_3)(4,5\text{-diphenylisoxazole})]$ (74), prepared by the cycloaddition reaction of metal-coordinated phenylethyne with benzonitrile oxide, was found to be inert to ring-opening on treatment with BuLi [89JOM(372)287].

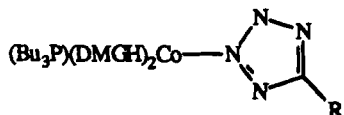
6. Tetrazoles

Deprotonation of 5-substituted tetrazoles yields the symmetrical tetrazolato anion, which reacts with alkylating agents to give both the 1,5- and the 2,5-disubstituted products. The anion can also coordinate to transition



(74)

metals via both N-1 and N-2, and rate data for some linkage isomerization processes have been reported (see Section II). A study of a number of 5-alkyl and aryl-substituted tetrazolate complexes $[\text{Co}(\text{Bu}_3\text{P})(\text{DMGH})_2(5\text{-Rtetrazolate})]$ (75) (DMGH = the monoanion of dimethylglyoxime) showed the tetrazolate ligand to bind solely through N-2 as a result of steric factors, and treatment of these complexes with alkylating agents gave the difficult to prepare 1,5-disubstituted tetrazoles exclusively (80JA2968).



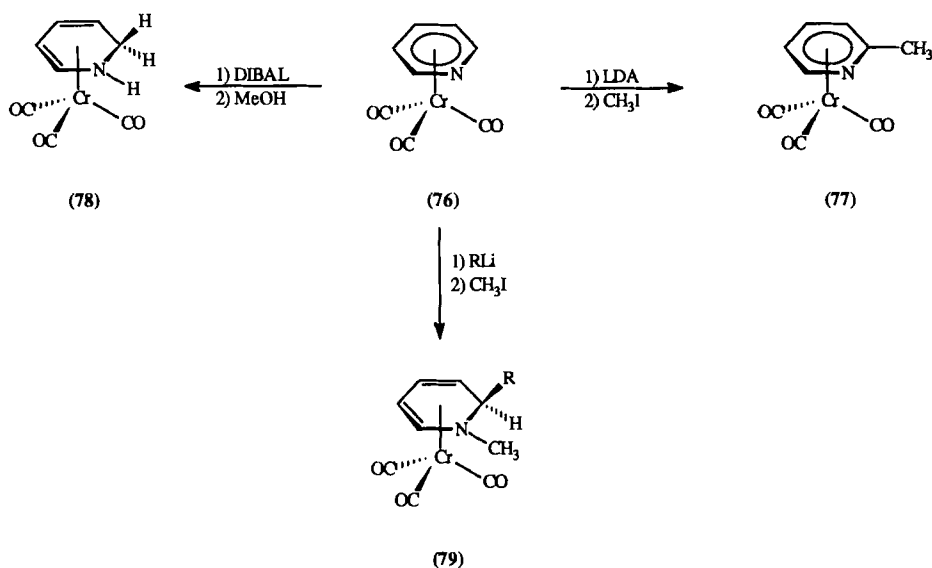
(75)

B. SIX-MEMBERED RINGS

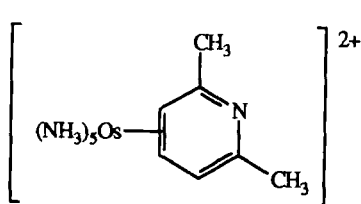
Pyridines

Pyridine and its derivatives form a vast number of transition metal complexes and the 2,2'-bipyridine ligand in particular has been extremely useful in the synthesis of complexes containing metal ions in both high and low oxidation states. In the majority of these complexes, the pyridine ligand is σ -bound to the metal ion through the nitrogen atom, although several cases of π -bound pyridines have recently been reported (88CC711) and some reactivity studies of these unusual complexes have been made. Reaction of $\text{Cr}(\text{CO})_6$ with the sterically hindered ligand 2,6-bis-(trimethylsilyl)pyridine prevented coordination at the nitrogen atom and gave the π -bound complex $[\text{Cr}(\text{CO})_3(\eta^6\text{-C}_5\text{H}_5\text{N})]$ (76) in good yield

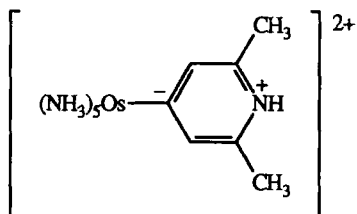
following desilylation. This complex gave the 2-methyl derivative (**77**) exclusively on sequential treatment with lithium di-isopropylamide and methyl iodide, whereas the 2,6-bis(trimethylsilyl) complex gave the analogous reaction at the 4-position (Scheme 20). Coordination was also found to activate the pyridine ring to a number of novel reactions involving disruption of the aromatic π -system. Reduction of the ligand was accomplished on reaction with di-isobutylaluminium hydride and quenching with MeOH to give the coordinated 1,2-dihydropyridine (**78**), which remains a six-electron donor through coordination of the nitrogen lone pair. Similar nucleophilic addition reactions occurred on treatment of **76** with alkyl lithium reagents and quenching with methyl iodide. In these cases, the coordinated *N*-methyl, *exo*-2-alkyl-1,2-dihydropyridine complexes (**79**) were isolated, in which nucleophilic attack occurred from the less hindered uncomplexed face of the pyridine ligand (Scheme 20). These products are of great interest, as the free ligands are very unstable (89CC995). Complexes of pyridines bound η^2 to the metal ion have also been recently prepared; again 2,6-disubstitution of the pyridine ligand prevents N-coordination and the η^2 -bound 2,6-lutidine complex (**80**) was isolated on reaction of this ligand with $[\text{Os}(\text{NH}_3)_5(1,2,3,4\text{-tetramethylbenzene})]^{2+}$ (87JA8101). This species rearranged in solution (hours) to give a σ -bound isomer (**81**) in which the metal ion was coordinated via C-4 and the nitrogen



SCHEME 20

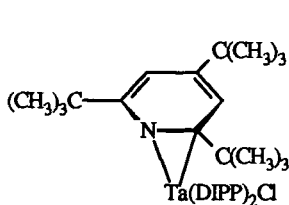


(80)



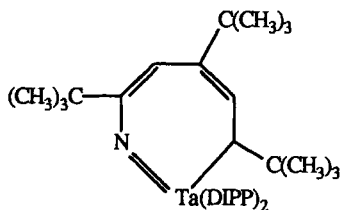
(81)

atom was protonated by the displaced hydrogen ($\text{p}K_{\text{a}} > 12.4$). An intramolecular rearrangement of the complex also occurred on electrochemical oxidation to give the N-bound Os(III) species. N-protonation and N-methylation of the free pyridine ligands were also used to prevent N-coordination and allowed the synthesis of a number of pyridinium complexes in which the ligands (*N*-methyl pyridinium, pyridinium, 2,6-lutidinium, *N*-methyl-4-picolinium) were similarly bound η^2 to the metal ion (89JA2896). Complexes of the first three ligands reacted similarly to the 2,6-lutidine species, with C—H bond activation occurring to give the C-4 bound ylide. The difference in reactivity of the *N*-methyl-4-picolinium complex was ascribed to the steric effect of the *para* substituents preventing σ -coordination of the metal at a carbon atom. An alternative mode of η^2 binding has been observed in the tantalum complex (82) in which the aromatic π -system has been disrupted. Reaction of this with the hydride donor LiBEt_3H resulted in facile ring-opening to give the unusual imido metallacycle (83) (92JA5462).



(82)

DIPP = 2,6-diisopropylphenoxide

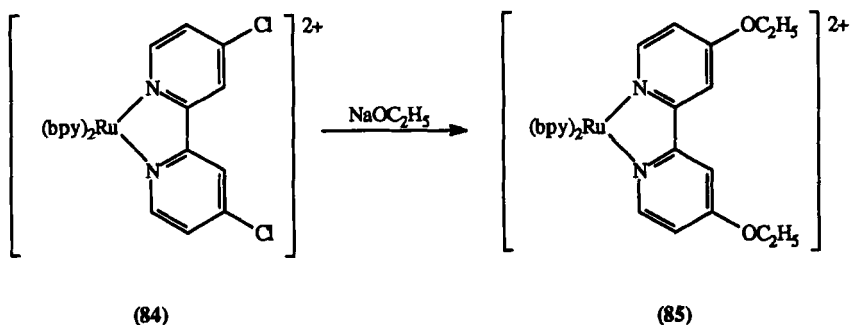


(83)

Although π -coordination of pyridines, either in an η^2 or η^6 fashion, dramatically influences the reactivity of the ligand, the same is not true of σ -bound pyridines and only in a few cases have unusual reactions of these complexes been observed. Pyridine is less reactive toward electro-

philic substitution at carbon than benzene and such reactions require very forcing conditions and give low yields of product. The N-coordinated ligand has been found to behave in a similar fashion, with no activation toward electrophilic attack being observed. Thus $[\text{Cr}(\text{C}_5\text{H}_5\text{N})_3\text{Cl}_3]$ was found to be inert to both chlorination in refluxing nitrobenzene and nitration in refluxing HNO_3 containing BF_3 (60JA4196). $[\text{Co}(\text{NH}_3)_5(\text{C}_5\text{H}_5\text{N})]^{3+}$ is similarly inert to nitration, as are the 3- and 4-methylpyridine congeners. These observations were attributed to the presence of a ligand LUMO node at the heteroatom that prevents $d-\pi^*$ electron donation from the metal ion and thus renders the $\text{Co}(\text{NH}_3)_5^{3+}$ moiety strongly electron-withdrawing (91IC4374). A study of the complex $[\text{Cu}(\text{8-hydroxyquinoline})_2]$ showed a number of electrophilic substitution reactions (benzoylation, sulfonation, nitration, thiocyanation, mercuration, and iodination) to occur at the ring, although the reactivity of the metal complex was in all cases similar to that of the free ligand (64IC1549). However, $[\text{Co}(\text{phen})_3]^{3+}$ and $[\text{Fe}(\text{phen})_3]^{3+}$ were found to be significantly more reactive toward nitration in $\text{HNO}_3/\text{H}_2\text{SO}_4$ than the free ligand, metal coordination preventing deactivating protonation of the heteroatoms under the highly acidic conditions used [63CI(L)1727].

Although Gillard's hypothesis of covalent hydration of metal-coordinated pyridines by nucleophilic attack of OH^- ion remains unproven (see Section IV) there are instances where metal-coordination results in activation of the heterocyclic ligand toward nucleophilic substitution. Thus, although 4,4'-dichloro-2,2'-bipyridine fails to react with sodium ethoxide in refluxing EtOH, the complex $[\text{Ru}(\text{bpy})_2(4,4'-\text{Cl}_2\text{bpy})]^{2+}$ (**84**) reacted to give quantitative formation of the 4,4'-diethoxy species (**85**), formed by nucleophilic displacement of chloride (Scheme 21) (84MI5). Similar reaction of the bound ligand was also observed with other nucleo-



SCHEME 21

philes (OH^- , SO_3^{2-} , alkylamines) under conditions where the free ligand failed to react. Interestingly, the reaction with OH^- gave no evidence of attack at C-6, giving only the 4,4'-dihydroxy species after acidification. The reaction with a number of di-, tri-, and tetraamines was investigated in a subsequent paper and in all cases good yields of the diamino complex were obtained (88MI3).

The influence of metal-coordination upon bipyridine ligands has also been demonstrated by the observation of proton exchange in strongly basic solutions. In contrast to the free ligand where no reaction is observed, both $[\text{Ru}(\text{bpy})_3]^{2+}$ and $[\text{Os}(\text{bpy})_3]^{2+}$ were found to undergo proton exchange primarily at the 3,3' positions on treatment of DMSO solutions with CH_3O^- or OH^- [82CC34; 86JCS(D)1993], with the order of reactivity for the Os(II) complex being $3,3' \gg 5,5' > 6,6' > 4,4'$. In these cases the difference in reactivity between the free and the bound ligands is possibly related to the fact that the free ligand preferentially adopts the *trans* conformation, thus avoiding steric interactions between the 3 and 3' protons. Coordination to a metal ion necessarily forces the ligand into the *cis* conformation, thereby bringing the 3 and 3' protons into close proximity. Proton exchange at the bipyridine ligand has also been observed in the $[\text{Rh}(\text{bpy})_3]^{3+}$ cation (89MI4) and in the Pt(IV) complex $[\text{Pt}(\text{bpy})(\text{tach})(\text{H}_2\text{O})]^{4+}$ (tach = 1,3,5-triaminocyclohexane) (90IC1958), although in both cases preferential reaction occurred at the 6,6' positions. Rate data for the platinum complex showed pH-independent regions that were interpreted as resulting from intramolecular catalysis by a deprotonated NH_2 group of the tach ligand, and this is further evidence that the observed proton exchange in these complexes is simply an acid/base reaction in which metal-coordination enhances the acidity of the ligand protons, rather than occurring as a result of cyclometallation or nucleophilic attack on the ligand.

Direct ethylation at the 5-position of coordinated 2,2'-bipyridine has been observed on irradiation of $[\text{fac-Re}(\text{bpy})(\text{CO})_3\text{Br}]$ and triethylamine in DMF (87CC1153). This reaction was postulated to occur via a mechanism involving reduction of the ligand to the radical anion.

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The Chemistry of Unsaturated Nitrogen-Heterocyclic Compounds Containing Carbonyl Groups

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Most hydroxy-substituted azaheteroaromatic compounds exist predominately in the NH/carbonyl tautomeric form, and such compounds have been widely discussed. By contrast, aza derivatives of cyclopentadienone, and of quinones, although they have received considerable attention in the last 30 years, have never previously been reviewed. In the present overview, we have attempted to collect the information on such derivatives, as well as including 1-azetin-4-ones, i.e., of those azaheterocycles which contain in the ring at least one carbonyl group and one or two nitrogen atoms in the form of C=N or N=N bonds. Many of these compounds are unstable but their importance as reactive intermediates is established and many of them could be used as synthons in the preparation of pharmacologically active compounds.

I. Four-Membered Rings with One Nitrogen Atom

A. EXISTENCE AND STABILITY

1-Azetin-4-one (**1**) had been postulated by several authors as an intermediate in the reactions of 4-substituted azetidin-2-ones (**2**) in which substituents at position 4 were formally substituted by nucleophiles. The mechanism of these substitutions has been investigated by Fedor (84JOC5094), who has proposed that reaction occurs by an E1cB elimination–addition pathway in which an azetidinone anion and, by implication, a 1,4-unsaturated azetinone (**1**) are intermediates (90JOC5655). In aqueous sodium hydroxide the initial product is probably the 4-hydroxyazetidinone, which fragments to the 3-hydroxyacrylamide anion.

The free existence in solution of 1-azetin-4-one has been demonstrated for the first time by using the three-phase test (90JOC434). The intermediate was generated from a 4-polymeric sulfonate 2-azetidinone, which is able to act as its nonpolymeric analogue 4-acetoxy-2-azetidinone in reactions with nucleophilic compounds.

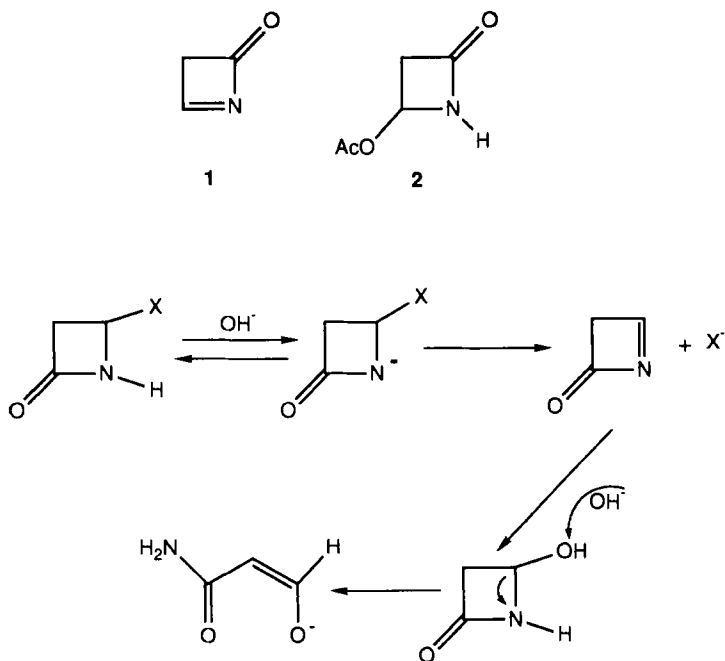


FIG. 1.

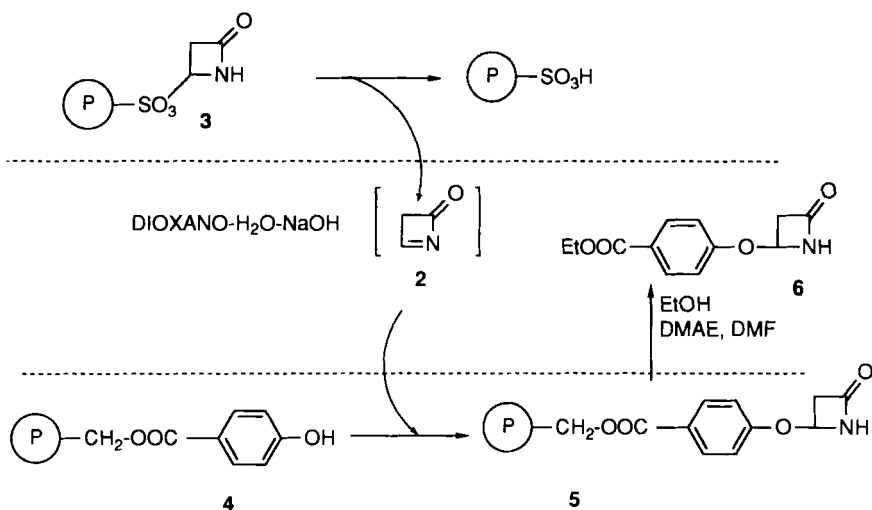


FIG. 2.

Another pathway to products (5) and (6) could be a 3,4-elimination, which generates an unsaturated β -lactam isomeric with (1). Apart from the fact that the N-proton is the easiest proton to be transferred, Fedor (84JOC5094) demonstrated that 3,3-dimethyl derivatives of 4-(aryloxy)azetidin-2-ones showed the same behavior with alkali as the 3-unsubstituted compounds. Thus, 1,4-elimination must be the main process.

For *N*-alkyl or *N*-aryl β -lactams, substitution at the 4-position must involve either elimination-addition via an azetinone containing a 3,4 carbon-carbon double bond (7 \rightarrow 8 \rightarrow 9) or direct displacement by $\text{S}_{\text{N}}2$ (7 \rightarrow 9) or $\text{S}_{\text{N}}1$ (7 \rightarrow 10 \rightarrow 9) mechanisms. The elimination-addition pathway would again presumably occur by an E1cB mechanism, but with anion formation now occurring at the 3- rather than the 1-position (90JOC3244).

The possibility of carbon-carbon double bond formation within a β -lactam ring is suggested by the known tendency of penicillins with electron-withdrawing substituents such as *p*-nitrophenylimino or phthalimido at the 6-position to undergo base-promoted rearrangement to thiazepinones, a reaction for which an azetinone is reasonably proposed as an intermediate (71CC647).

Despite the strong implications of the thiazepinone rearrangement of penicillins that elimination can occur in the β -lactam ring, no example of this reaction has been uncovered for monocyclic β -lactams, even for a leaving group as reactive as chloride. In basic solutions hydrolysis or methanolysis of the β -lactam ring takes precedence. The only reaction

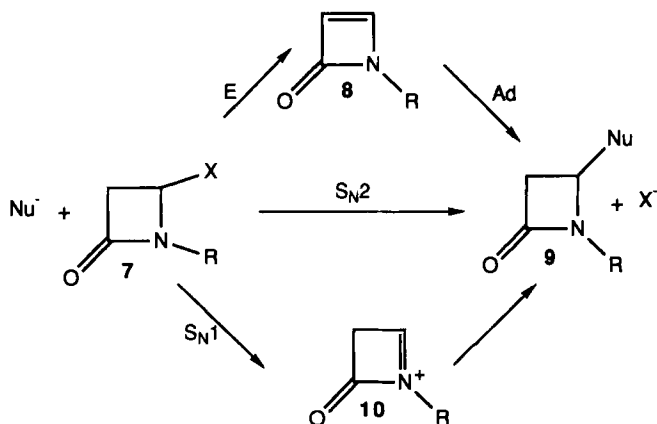


FIG. 3.

competing with ring-opening is solvolysis, and this leads to substitution rather than elimination products. One way of avoiding ring-opening would be to use amine bases in aprotic solvents. These are the conditions under which the thiazepinone rearrangement is observed. So far, however, even the chloro substrates have proved unreactive under these conditions.

1-Azetin-4-one seems to be a highly unstable intermediate with a lifetime of 2.0 ± 0.5 s. This instability could be ascribed not only to the high strain of the four-member ring, but also to the easy conversion of (1) into open 3-hydroxyacrylamide oxyanion. By using an UV rapid spectra detector a UV spectrum of intermediate (1) was obtained that showed a wavelength of 246 nm.

B. REACTIVITY OF 1-AZETIN-4-ONE WITH NUCLEOPHILES

After free existence of 1-azetin-4-one had been demonstrated, it seems that the mechanism of the so-called nucleophilic substitution reactions of 4-substituted 2-azetidinone follows an elimination–addition pathway. The intermediacy of (1) in displacement reactions is fully consistent with the stereochemistry of the reaction (83CJC1899; 91TL2265).

The displacement of the acetoxy group in 4-acetoxy-2-azetidinone (2) can be carried out by many nucleophilic systems such as thiols, thioacids, alcohols (74LA539), carbon nucleophiles (80H575), carboxylic acids (81H243), tertiary carbanions (81TL1161), nitrogen nucleophiles (81H1487), or oxygen and phosphorus nucleophiles [82H(17)463; 82H(19)1853].

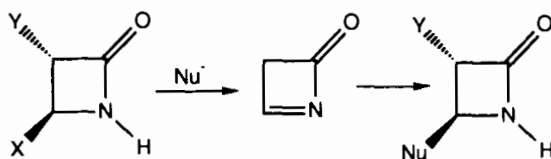


FIG. 4.

Treatment of 4-phenylsulfonylazetidine-2-one with di-*n*-butyl-copper-lithium in tetrahydrofuran gave 4-*n*-butyl-azetidin-2-one in 94% yield; the same product was also obtained from the reaction of 4-acetoxiazetidin-2-one with di-*n*-butyl-copper-lithium in 89% yield. In contrast with the lithium organocuprate, Grignard reagents showed considerable differences in the reaction with both compounds. Thus 4-ethylazetidin-2-one was obtained in 74.2% yield by treatment of (13a) with ethylmagnesium bromide in THF, whereas the same reaction starting from (14) gave the product in only 12.4% yield. Analogously, 4-vinyl-, 4-allyl-, and 4-

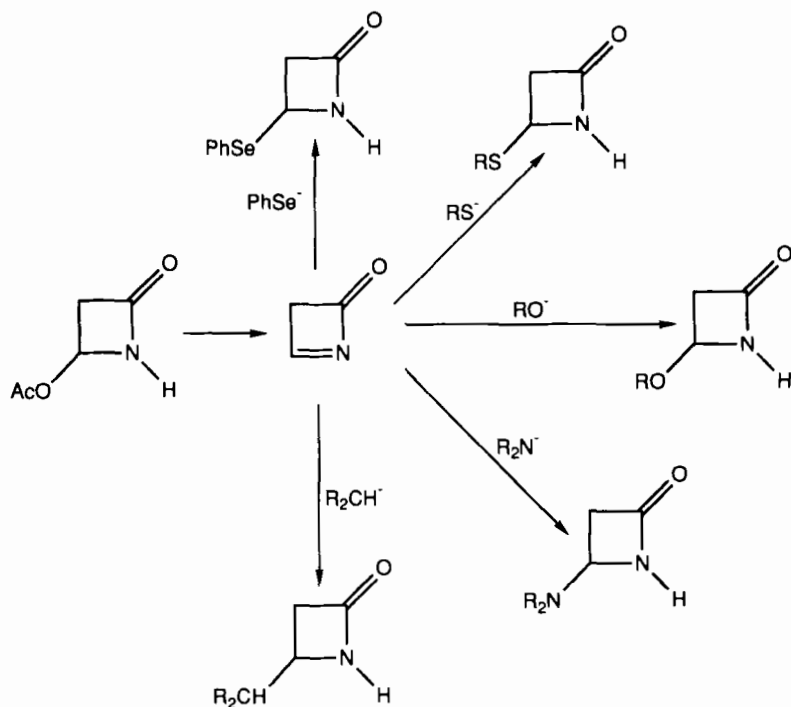


FIG. 5.

TABLE I
REACTIONS OF 4-PHENYLSULFONYL- AND 4-ACETOXYAZETIDIN-2-ONE WITH
ORGANOMETALLIC REAGENTS

Product	Reagent	Yield from 11a (%)	Yield from 12 (%)
13a	LiCu(Bu ⁿ) ₂	94.0	89.0
13b	EtMgBr	74.2	12.4
13c	H ₂ C=CHMgBr	65.5	3.4
13d	LiCu(CH ₂ CH=CH ₂) ₂	100.0	—
13d	CH ₂ =CH—CH ₂ MgCl	54.9	—
13e	EtOC≡CMgBr	95.4	—
13f	PhSC≡CMgBr	78.9	—

ethyl-azetidin-2-one derivatives were synthesized by treatment with the corresponding Grignard reagents or organocuprates (Table I). When the starting azetidin-2-one has a substituent at the 3-position, both *trans* and *cis* compounds were obtained (80CC736).

One exceptional reaction was observed; the reaction of (**13a**) with the Grignard reagent of *t*-butyl acetate (BrMgCH₂-CO₂Bu^t) afforded the bisazetidinone (**14**) in 51.7% yield without the desired product. The reactions described here strongly suggest a 1,4-addition of the organometallic reagents to the intermediate azetinone, derived from 5-membered (**15**) or 6-membered (**16**) coordination compounds.

C. REACTIVITY OF 1-AZETIN-4-ONE WITH DIENES

[2 + 4] cycloaddition of dienes to activated imines has been well documented (79H949). Thus, Danishefsky and Kerwin have reported the Lewis acid-catalyzed cyclocondensation of nonactivated imines with a siloxydiene to give hetero Diels–Alder adduct under mild conditions (85TL1277). In a similar way 1-azetin-4-one generated from 4-acetoxy-2-azetidinone has been trapped as a cyclocondensation adduct using siloxydienes in the presence of a Lewis acid.

The siloxydiene (**17a**) derived from methyl vinyl ketone was subjected to a ZnCl₂-mediated reaction with 4-acetoxy-2-azetidinone (**18**). The reaction under different conditions gave a cyclocondensation adduct (**19a**) as well as the displacement product (**20a**). Trimethylsilyl trifluoromethanesulfonate as a catalyst in place of ZnCl₂ failed to give any cycloaddition adduct, producing only a 4-substituted azetidinone (**20a**) in low yield. The siloxydiene (**17b**) derived from *trans*-pent-3-en-2-one also successfully trapped the azetinone as a cycloadduct to give 4*b*-methyl-carbaceph-2-em (**19b**)

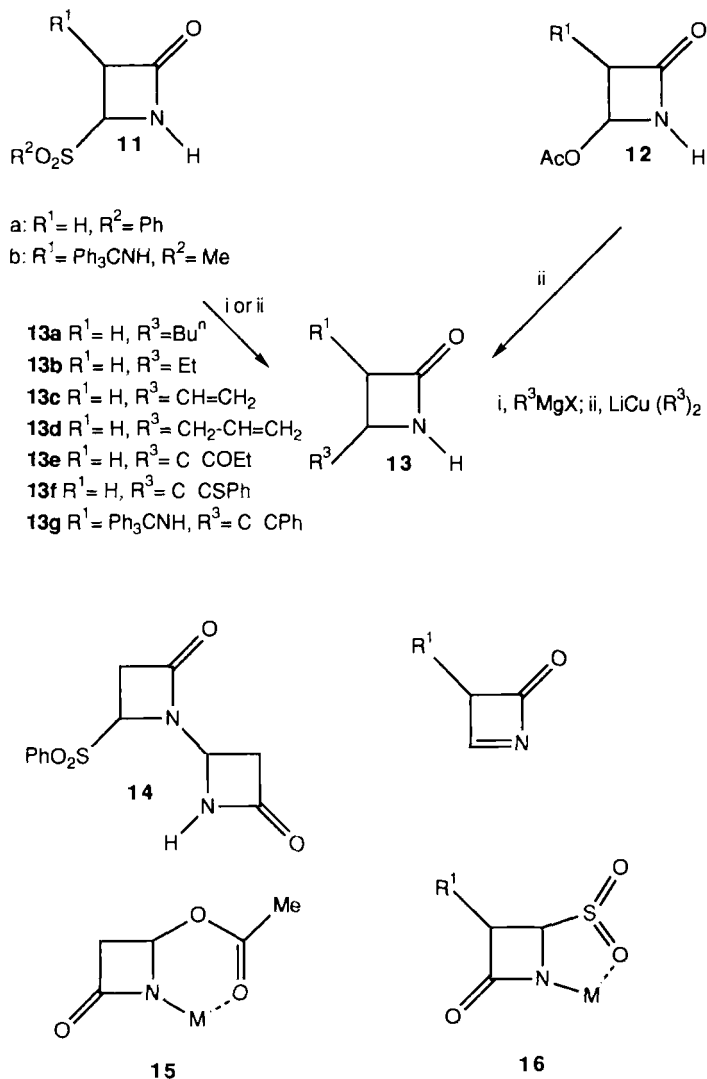
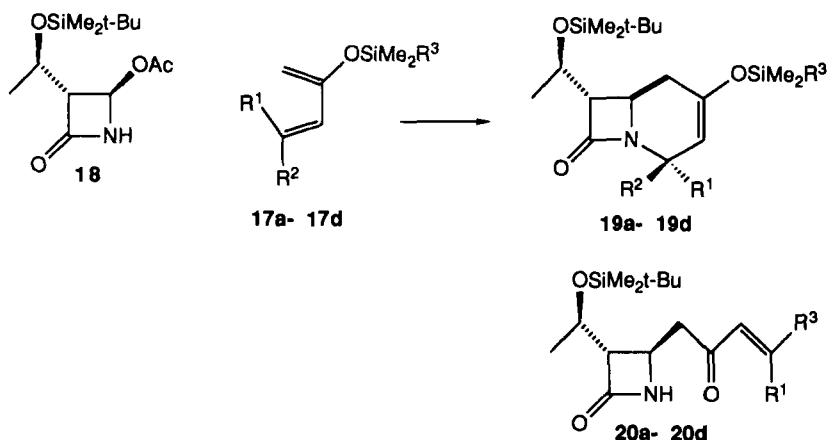


FIG. 6.

as a major stereoisomer. The stereoselectivity observed in this reaction may be explained by the *endo* addition of the imine to the siloxydiene or a stepwise mechanism through a chair-like transition state. It is not certain whether the mechanism is a [4+2] cycloaddition or stepwise process (85TL6309).



	Conditions	Yield	
		19	20
a: R ¹ =R ² =H, R ³ =Me	ZnCl ₂ /CH ₂ Cl ₂ , r.t.	16	37
	ZnCl ₂ /CH ₃ CN, reflux	18	75
	Me ₃ SiTf/CH ₂ Cl ₂ , r.t.	0	18
b: R ¹ =H, R ² =R ³ =Me	ZnCl ₂ /CH ₃ CN, reflux	20	47
c: R ¹ =H, R ² =Ph, R ³ =t-Bu	ZnCl ₂ /CH ₂ Cl ₂ , r.t.	0	72
d: R ¹ =R ² =R ³ =Me	ZnCl ₂ /CH ₃ CN, reflux	0	48

FIG. 7.

Trapping of 1-azetidin-4-one as a dienophile was attempted by using some polymers functionalized with dienic groups, such as the 2-(polymeric carbomoxymethyl)-3-methyl-1,3-butadiene of the polymeric ester of 2-furoic acid, which have been good trapping agents for other dienophilic systems. Under several experimental conditions, both dienic polymers were recovered unchanged.

The three-phase test has been used to distinguish between associative and dissociative mechanisms. Thus, in this case the negative results in the trapping of the intermediate with dienic polymers seem to support a stepwise mechanism in the formation of cyclocondensation adducts with siloxydienes and 1-azetidin-4-one.

D. SYNTHETIC APPLICATIONS

β -Lactams are a group of antibacterial agents of unparalleled importance in medicine. In consequence of this outstanding activity and in recognition of their molecular structures, β -lactams have been subjected to extensive

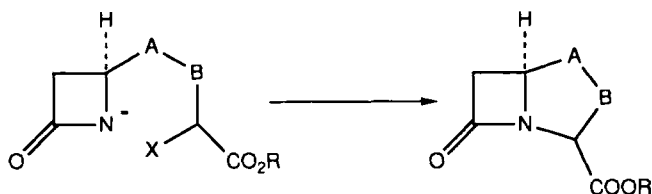


FIG. 8.

synthetic investigations for over 40 years. These studies have led to the design and assembly of superior penicillins (79TL3867), cephalosporins, carbapenems, monolactams, and numerous nonnatural analogues [80JCS(P1)2222; 82TL2293, 82TL3921]. Many bioactive β -lactams are bicyclic and usually contain a five- or six-membered ring fused to the β -lactam nucleus (82TL379). In principle such systems should be available from the intramolecular N-alkylation of a monocyclic β -lactam system (79CC532). This kind of system could be obtained from azetidin-2-one 4-substituted with nucleophiles as previously indicated (90JOC5110, 90TL2637; 91TL2375).

II. Five-Membered Rings with One Nitrogen Atom

A. 1-AZOLIN-5-ONES

1-Azolin-5-one (**21**) is an unstable system with a lifetime of 5.5 s. Its existence and reactivity have been demonstrated by using a polymeric system (**22**) as an intermediate precursor and also polymeric trapping agents in the three phase test. This reactive intermediate is able to react with nucleophiles in a manner similar to that of the four-member ring counterpart, 1-azetin-4-one. 1-Azolin-5-one is able to react with dienic trappings to give the Diels–Alder adducts; this behavior is different from that observed in the four-membered ring intermediate when both reactions were carried out under identical experimental conditions. (90JOC434)

Substituted 1-azolin-5-ones have been described; thus, 2-ethoxy-1-azolin-5-one (**24**) is a stable compound that has been prepared from succinimide [80OS(59)132]. 2-Ethoxy-1-azolin-5-one undergoes a photochemical ring contraction giving cyclopropanone derivatives. The photochemical reaction of (**24**) in *tert*-butylalcohol as solvent yield *tert*-butyl *N*-(1-ethoxycyclopropyl)cabamate (**25**).

Other substituted 1-azolin-5-ones have been proposed in different reactions. One of them is the reaction between *N*-aryl- α -iminoketones and

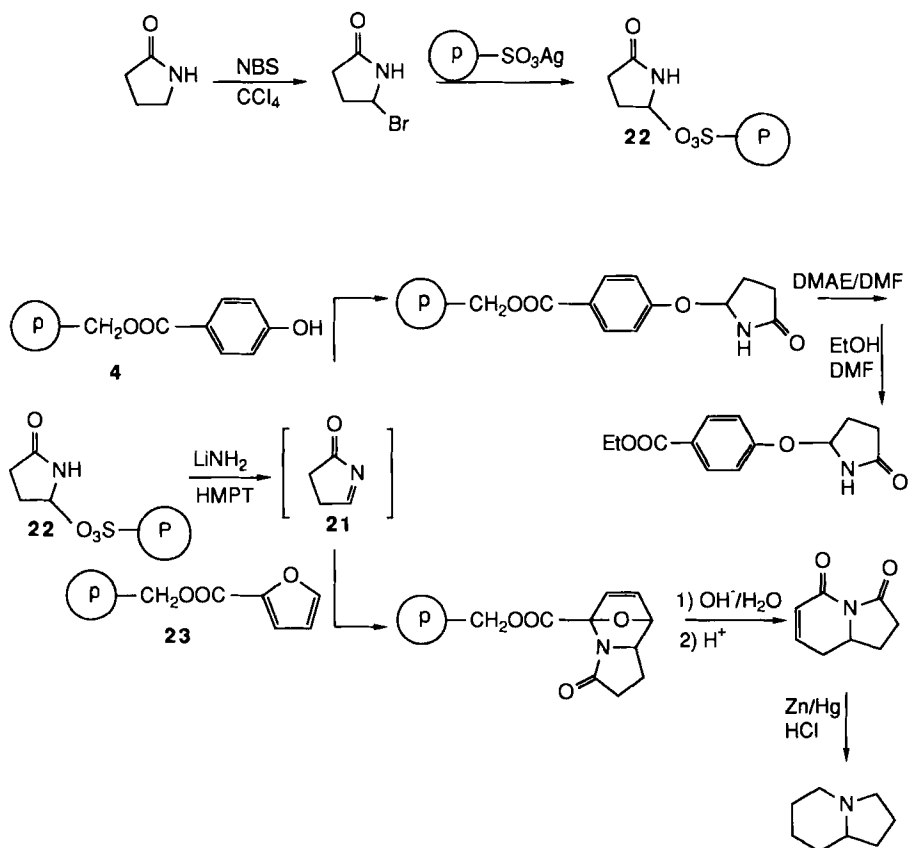


FIG. 9.

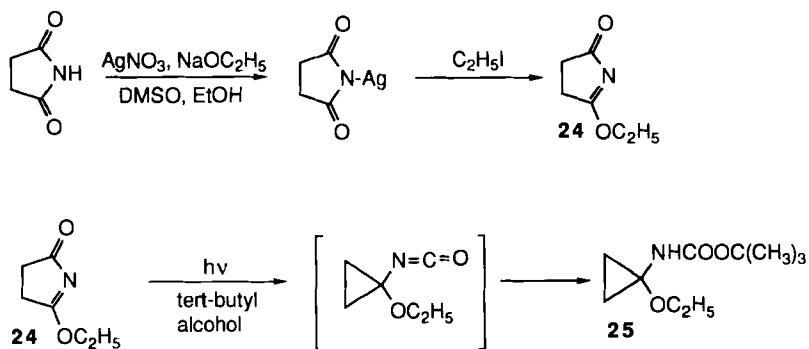


FIG. 10.

simple lithium ester enolates to give β -hydroxy- γ -imino esters in a totally site-selective addition to the carbonyl group (85TL4403). By reaction of silylimine (**26**) prepared *in situ* from benzyl and lithium hexamethyl disilylamide, with simple α -lithiated esters (**27**) it is possible to obtain the N-silylated β -hydroxy- γ -imino esters (**28**) and the polyfunctional azolines (**29–32**), depending on the nature of the enolate and on the experimental conditions. Thus, enolate (**27b**) gives (**30**) exclusively. Formation of products (**31**) and (**32**) from enolate (**27b**) may be accounted for through the corresponding compound (**30**). Base-induced elimination of the trimethylsilyloxy group in (**30**), via anion (**33**), presumably through a E1cB mechanism, could afford aza-annulenone (**34**) as an unstable intermediate, which would finally add Me_3SiO^- to the $\text{C}=\text{N}$ group to give amide (**35**).

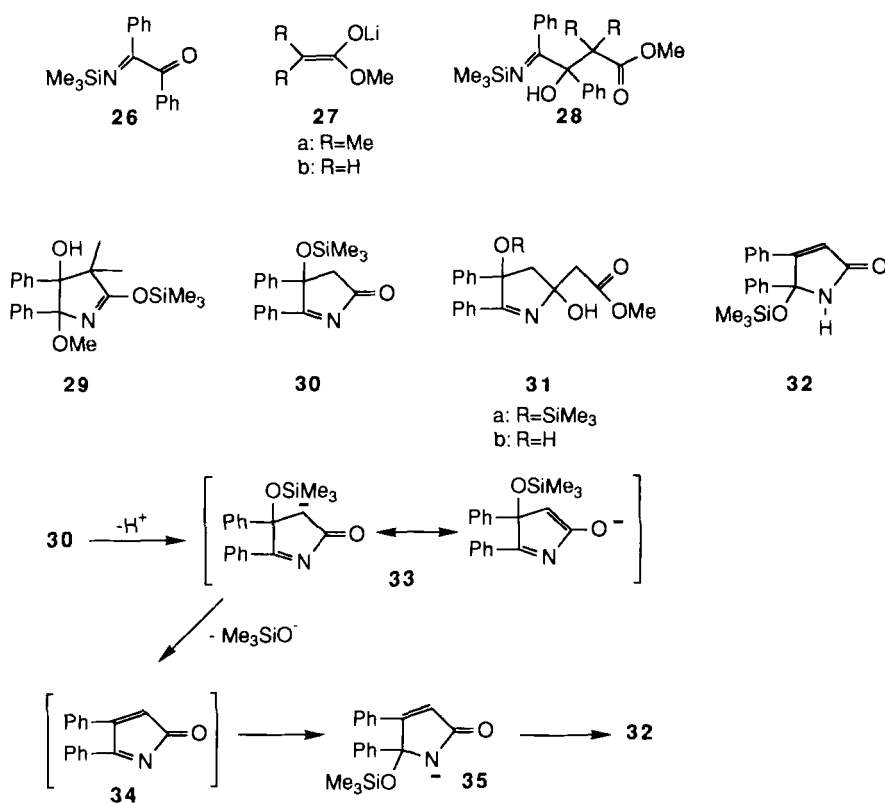


FIG. 11.

B. 2-AZA- AND 3-AZA-2,4-CYCLOPENTADIENONES

2-Aza-2,4-cyclopentadienone and 3-aza-2,4-cyclopentadienone are two reactive intermediates (75AG38) whose existence has been demonstrated by using the three-phase test. The precursor polymers for both compounds have been prepared: (36) from maleimide, which was reduced with LiAlH_4 and linked to the sulfonic polymer, and (39) by reaction between (37) and (38) (88JA4017; 91JOC5417).

Both intermediates (40) and (41) are able to act either as dienes or as dienophiles in the Diels–Alder reactions. The Diels–Alder reactions have been carried out by using polymeric monoester of acetylenedicarboxylic acid (42) as a dienophile trapping agent and polymeric ester of 2-furoic acid (23) as a dienic trapping polymer (81JA1797).

When (36) reacted with polymeric monoester of acetylenedicarboxylic acid, a polymeric adduct was obtained. Saponification of this resin

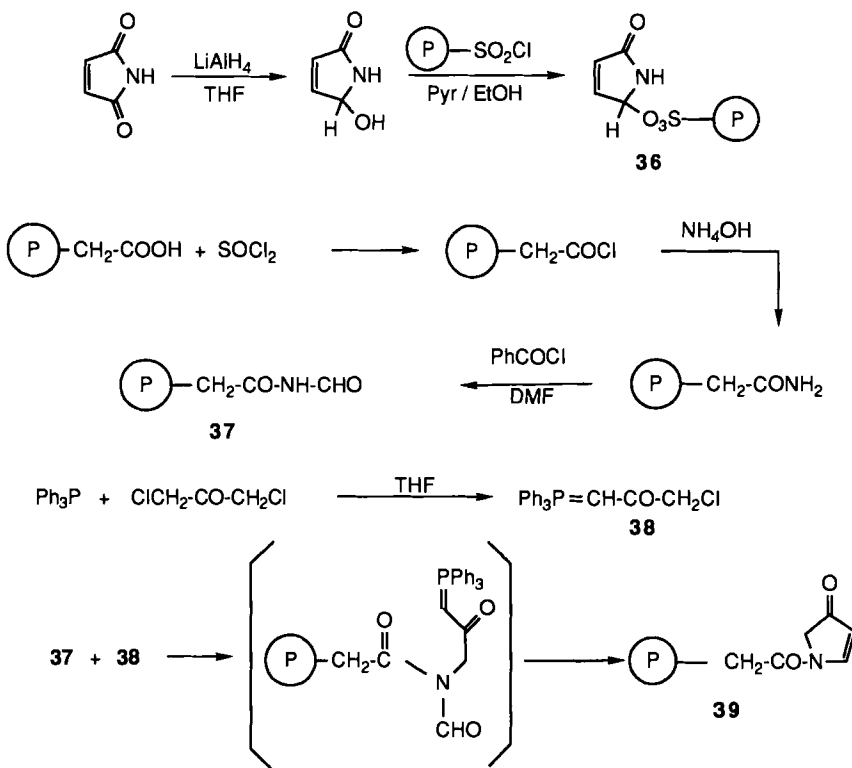


FIG. 12.

followed by acidification gave a mixture of acetylenedicarboxylic and pyridine-2,3-dicarboxylic acids. The formation of pyridine-2,3-dicarboxylic acid can be explained by the reaction of free 2-aza-2,4-cyclopentadienone with (42) followed by carbonyl extrusion and aromatization. When polymeric ester of 2-furoic acid (23) was used, polymeric adduct (43) was isolated, from which imidic diketone (44) was obtained. A Clemmensen reduction of (44) gave δ -coniceine (45).

Similar results were observed when polymeric precursor (39) was used. Pyridine-2,3-dicarboxylic acid was the product of the reaction between trapping agent (42) and precursor (39). This compound could be explained, as below, by carbonyl extrusion and aromatization. When 3-aza-2,4-cyclopentadienone was generated in the presence of trapping agent (23), compound (46) was isolated after the reaction. The reduction of (46) gave δ -coniceine.

Lifetime determinations have demonstrated that the position of the nitrogen atom has a strong influence on the stability of these intermediates. Thus, 2-aza-2,4-cyclopentadienone has a lifetime around 2 s, whereas the 3-isomer lifetime is 11 s, similar to that of the carbocyclic counterpart. These values seem to depend on the high reactivity of the *N*-acylimine group contained in 2-aza-2,4-cyclopentadienone.

III. Five-Membered Rings with Two Nitrogen Atoms

A. 2,3-DIAZA-2,4-CYCLOPENTADIENONES

The existence of several diaza derivatives of 2,4-cyclopentadienone as reactive intermediates has been proposed by some authors [65CB3229; 66AG676; 70JCS(C)540]. Thus, transient formation of 4,5-diphenyl-2,3-diaza-2,4-cyclopentadienone in elimination reactions has been postulated as a result of trapping experiments with 1,3-butadiene or 1,3-cyclopentadiene, giving the appropriate Diels–Alder adducts (66JOC2867). Alkaline degradation of halopyrazolones convert them to unsaturated acids. It would be reasonable to expect that the first step would involve dehydrohalogenation to give the diazacyclopentadienone (47), which might undergo loss of nitrogen to give substituted cyclopropenone (48) [73JCS(P1)221]. However, no cyclopropenones have been isolated under the conditions of the reaction and, although authentic cyclopropenones were able to undergo ring opening with the formation of α,β -unsaturated acids, it was shown that such compounds could not be involved in the halopyrazolone reaction. A plausible scheme to account for these results is (49 \rightarrow 47 \rightarrow 50). The first step in the reaction is believed to involve elimination of halide

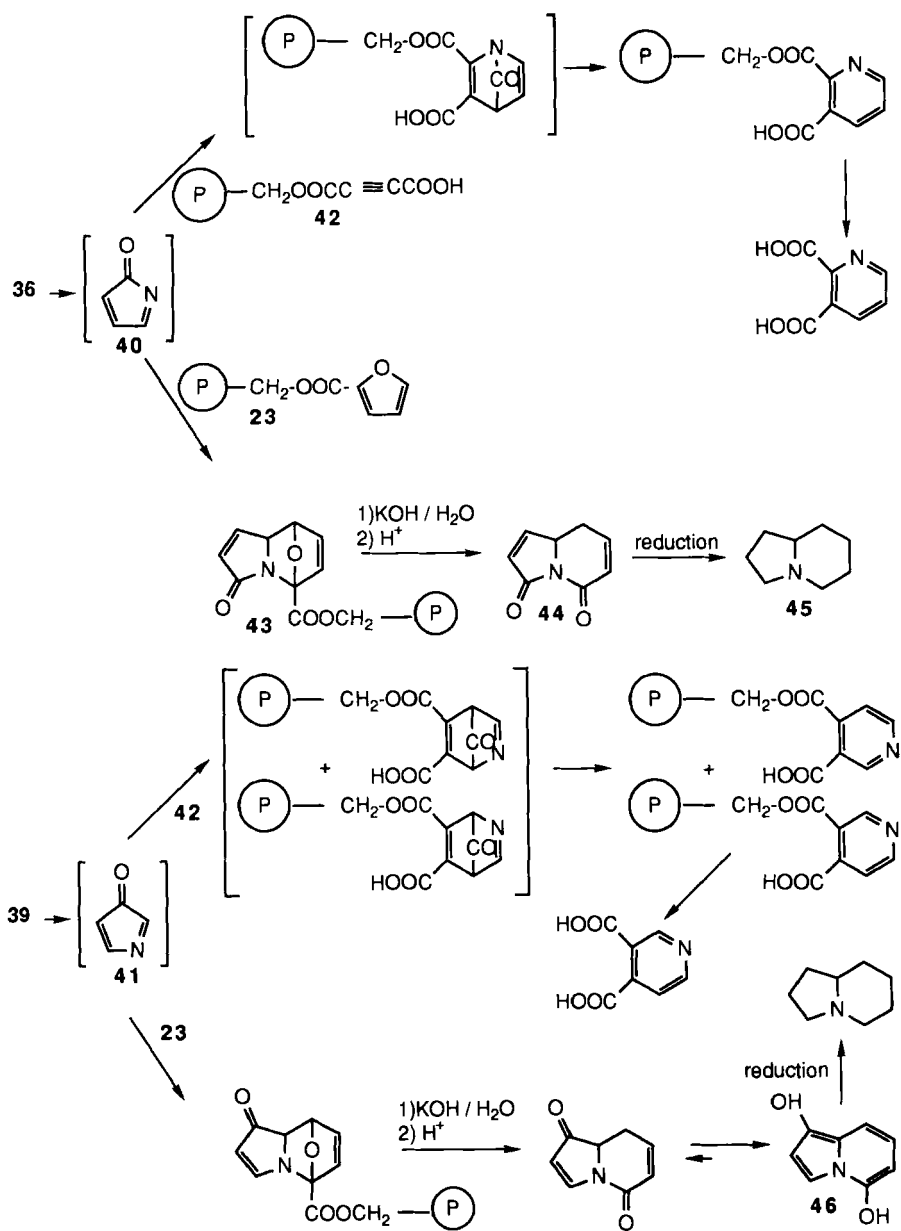


FIG. 13.

ion from anion (49) to give a diazacyclopentadienone intermediate (47). Ring opening of (47) by hydroxide ion with concomitant loss of nitrogen followed by appropriate protonation steps would yield the corresponding acids [87H(25)79].

Although it has not been possible to isolate the diazacyclopentadienone (47), indirect evidence for its involvement in this reaction has been obtained by trapping experiments. When an ether solution of 3,4-diphenyl-4-chloro-2-pyrazolin-5-one was treated with triethylamine in the presence of cyclopentadiene, an excellent yield was obtained of compound (51), which has been shown to be the Diels–Alder adduct. The unlikely possibility that (47) could have the alternative structure in which (51) acts as diene rather than dienophile can be excluded on the basis of the appearance of normal hydrazide carbonyl absorption.

On the other hand, unstable pyrazol-3-one ring systems have been formed *in situ* through the oxidation of substituted pyrazolin-3-ones with lead tetraacetate and have been trapped in the presence of dienes through the Diels–Alder reaction. It is known that the reactivity of azadienophiles is increased if the azo linkage is electron deficient and sterically unhindered. The reactivity of the ring system has been tested against dienes of different reactivities, and adducts were obtained with four reactive dienes, which include 1,4-diphenylbutadiene, 2,3-dimethylbutadiene, cyclopentadiene, and α -phellandrene, and with two less reactive dienes, cyclohexadiene and cycloheptatriene, which do not give Diels–Alder adducts with ethyl azodicarboxylate (67JOC3321; 72JOC1696). No adduction was observed with anthracene, 1,3-cyclooctadiene, and bicycloheptadiene, which have given adducts with certain other *cis*-azodienophiles. No adduct was obtained with bicycloheptadiene; the diene reacted with lead tetraacetate to give 2-*exo*-7-*syn*-norbornane-2,4-diacetate before it oxidized the pyrazolin-5-one. No reaction was observed with the very unreactive diene *trans*-muconic acid, but 2,5-dimethyl-2,4-hexadiene with (52a) and lead tetraacetate gave 3,3,6-trimethyl-2-isobutenyl-2,3-dihydropyrazolo[2,3-*b*]-1,3-oxazole.

The decomposition products obtained from the oxidation of these compounds with lead tetraacetate in the absence of a diene have not been determined. The intermediates decompose without evolution of a gas to give a dark solid that contains lead as either a salt or a complex. An organic material may be freed from lead but it was impossible to identify it.

It is evident that the pyrazol-3-one ring system is less reactive than other *cis*-azadienophiles. This is attributed to the fact that the azo linkage in (47) is not so electron poor as those in (53) and (54). The degree of substitution in the pyrazoline ring does not appear to hinder the oxidation,

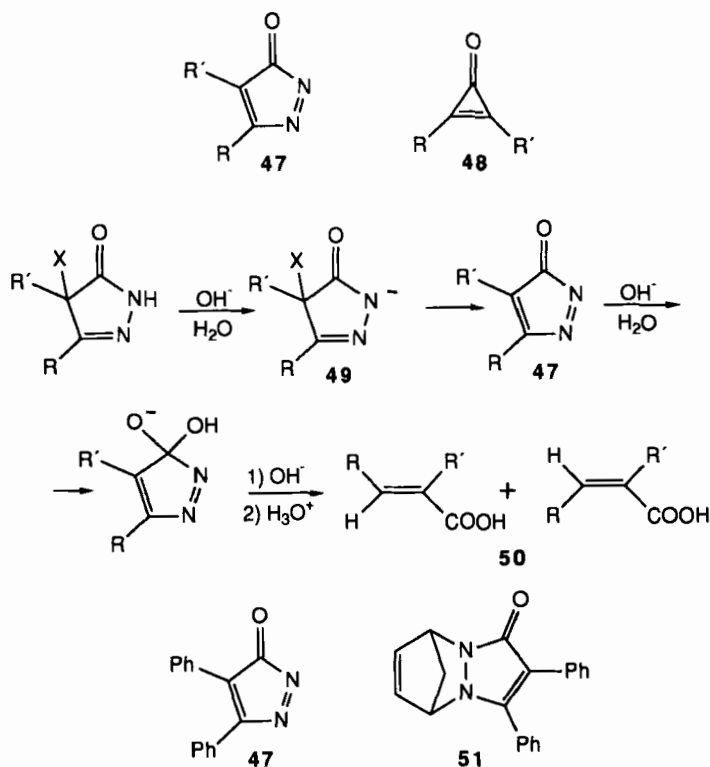


FIG. 14.

so that any 3,4-substituted pyrazolinone should react to give the pyrazol-3-one.

The oxidation of pyrazolinone (55) [85JCS(P1)71] in dichloromethane in the presence of isoprene gave a mixture of regioisomeric Diels-Alder adducts (57) and (58). By NMR the ratio was determined to be 5:4, although it was not possible to assign the major product by NMR. Reaction of compound (56) with 1-acetoxybutadiene, however, gave a single Diels-Alder adduct; attempts to purify the adduct by chromatography on silica gel resulted in hydrolysis and formation of the corresponding allylic alcohol. On the basis of its OH stretch in the IR spectrum at 3075 cm^{-1} , indicative of intramolecular hydrogen bonding, the alcohol was assigned the structure (60) and hence the initial adduct as (59).

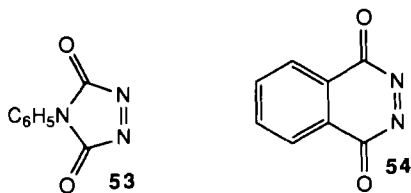
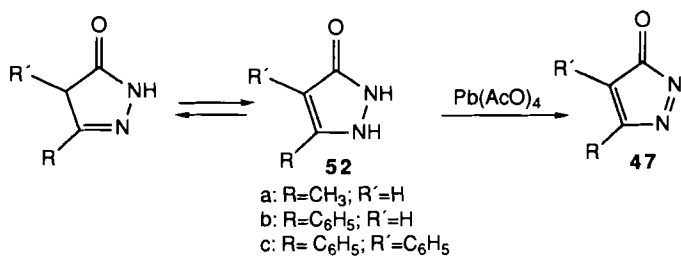


FIG. 15.

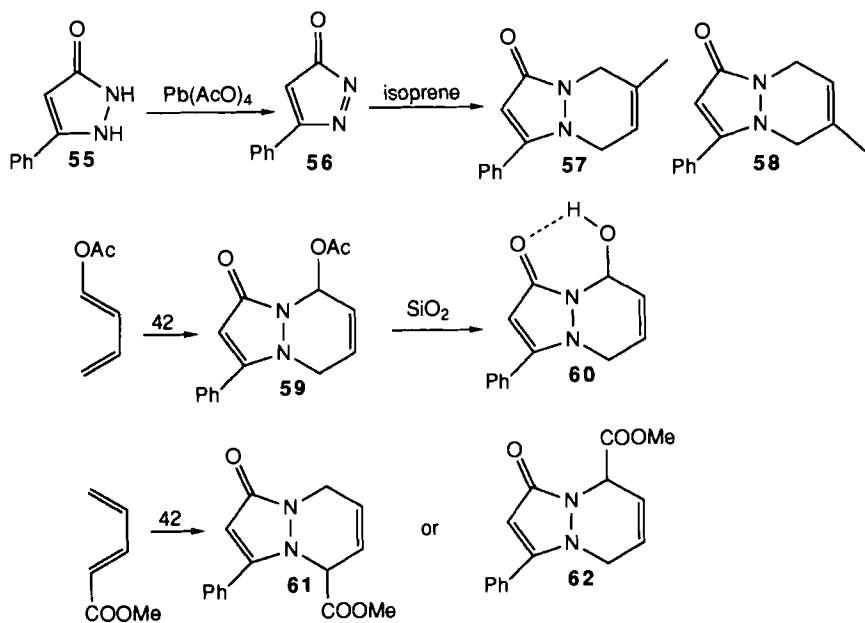


FIG. 16.

Methyl penta-2,4-dienoate also gave a single Diels–Alder adduct on reaction with azo dienophile (**57**). However, on the basis of the NMR spectral data the structure could not be assigned as (**61**) or (**62**) unambiguously. Thus, in common with the all-carbon Diels–Alder reaction, reactions of dienes containing conjugatively electron-releasing or -withdrawing groups with unsymmetrical azo dienophiles appear to exhibit high regioselectivity.

The existence of the unsubstituted intermediate (**63**) has been established by using the three-phase test (88JOC6112). As a polymeric precursor, the 2-polymeric sulfonamide of the 3-pyrazolin-5-one (**64**) was synthesized. Polymeric 2-(carboxymethyl)-3-methyl-1,3-butadiene was used as a trapping dienic polymer. After the usual working out the Diels–Alder adduct (**65**) was obtained from polymer via dealkylation. The formation of this adduct supports the free existence of 2,3-diaza-2,4-cyclopentadienone. Trapping of this intermediate as a diene was attempted by some polymers functionalized with dienophiles groups such as the polymeric monoester of acetylenedicarboxylic acid, and the polymeric benzylmaleimide. Under drastic conditions both polymeric dienes were recovered unchanged. Thus, 2,3-diaza-2,4-cyclopentadienones is able to act as an azadienophile, but not as an azadiene.

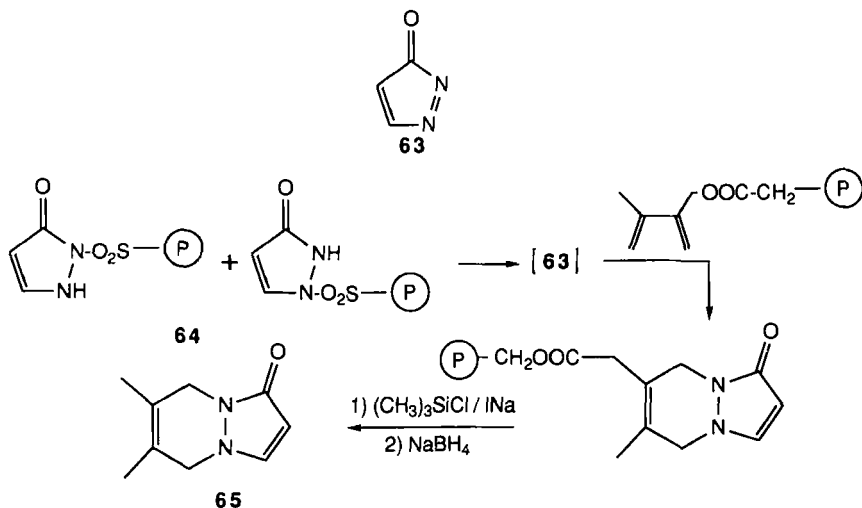


FIG. 17.

B. 3,4-DIAZA- AND 2,5-DIAZA-2,4-CYCLOPENTADIENONES

1,3-Diphenylpyrazol-4-ol (**66**) is oxidized to 2,5-diphenyl-3,4-diaza-2,4-cyclopentadienone (**67**) (78CJC904) by lead hydroxide in dry ether. It is a purple solid, deep red in acetonitrile and purple in concentrated sulfuric acid-acetonitrile mixtures, like tetraphenylcyclopentadienone in all these respects. However, unlike the carbocyclic compound, it has a barely detectable IR carbonyl band (at 1740 cm^{-1}) in the solid state. Weak IR bands are known to occur when the change in dipole moment during transition is close to zero and this could conceivably be the case for this intermediate, as the polarity of the CO bond would be greatly reduced compared to normal ketones by the contribution from the five resonance structures represented by (**68**) that are stabilized by virtue of the aromatic sextet and also the presence of the electronegative nitrogen atoms. The charges calculated for (**67**) and cyclopentadienone by the HMO method, although imprecise, clearly show the expected trend.

Generation of 2,5-diphenyl-3,4-diaza-2,4-cyclopentadienone can be effected in solution by thionyl chloride or by butyl nitrite, both of which have been used for analogous reactions (64JA5654). Solutions of (**67**) are very unstable at room temperature even in the dark and within 30 min are practically completely decomposed. A crystalline product may be isolated from the solution and had previously been tentatively assigned structure (**69**).

Two questions were of great interest in connection with the cycloaddition of (**67**). First its ability to react as a diene, as a dienophile, or as a

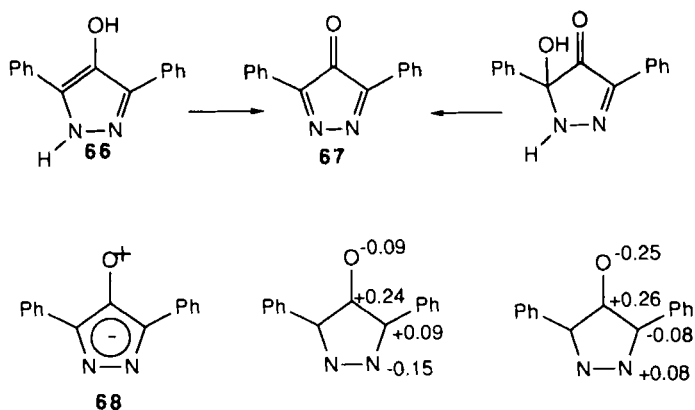


FIG. 18.

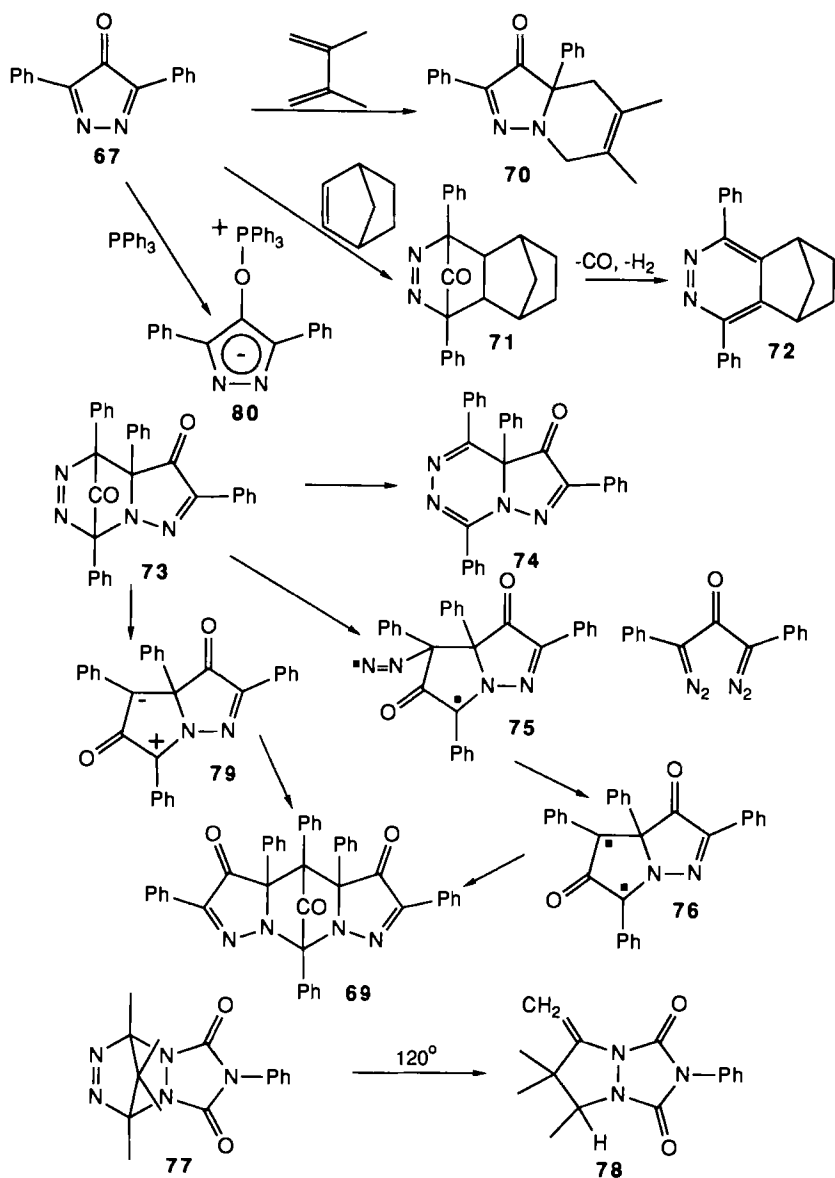
1,3-dipole and second if it reacts as a diene it could be an example of electron-deficient dienes which are highly reactive toward unactivated alkenes.

When (67) was treated with a wide variety of cycloaddition reagents under various conditions, it behaved as a diene or a dienophile but not as a 1,3-dipole. As a dienophile it reacted with 2,3-dimethyl-1,3-butadiene to give (70) and with cyclopentadiene to give an analogous product. As a diene it reacted with [2.2.1] bicycloheptene to give (72), presumably via (71), by loss of carbon monoxide and hydrogen. No products were isolated when (67) was treated with maleic anhydride, dimethyl acetylenedicarboxylate, diphenylacetylene, dimethyl fumarate, carbon disulfide, isobutyl vinyl ether, cyclohexene, and cyclopentene.

Although the diene and dienophile reactivities of (67) were anticipated, the self-condensation to give (69) is unusual. The first step, a simple Diels–Alder dimerization to give (73), is presumed but one would then anticipate formation of (74) by loss of carbon monoxide as normally observed for cyclopentadiene dimers. Instead nitrogen is lost. A possible explanation is that although carbon monoxide is lost by concerted reverse cycloaddition, nitrogen may be eliminated by two-step free radical process (73→75→76). There is a precedent for this mechanism in that (77) on heating is converted to (78) and a diradical intermediate analogous to (75) was proposed. The factor that encourages the free radical mechanism could be the presence of a stabilizing nitrogen substituent attached directly to the carbon radical generated in the initial bond-breaking step.

Note that this substituent is absent in (71) and hence the radical mechanism would be discouraged in favor of a concerted reverse cycloaddition. The final product (69) could then arise by two-step cycloaddition of (76) to another mole of (67). The above suggested mechanism has the advantage of avoiding symmetry problems associated with the simpler mechanism (73→79→69). If the latter mechanism is concerted according to the FMO theory, the overlapping lobes of the HOMO orbital of one reactant and the LUMO orbital of the other reactant should have the same phase. The coefficients of the HOMOs and LUMOSs of (67) and (78) reveal a mismatch for suprafacial attack and therefore the reaction is disallowed. Similarly, suprafacial extrusion of N₂ from (73) is disallowed.

The ability of (67) to react with [2.2.1] bicycloheptene but not maleic anhydride is intimately connected with its strong electron affinity and this property is further emphasized by the observation that it can oxidize hydrochloric acid to chlorine. When dry hydrogen chloride is passed through a solution of (67) in dry ether, chlorine gas is readily detected and a quantitative yield of 1,3-diphenylpyrazol-4-ol hydrochloride is produced. The low-intensity carbonyl IR band of (67) is a manifestation of the compa-



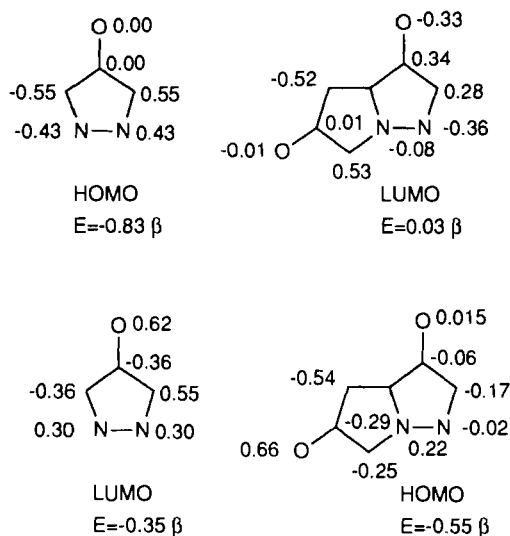


FIG. 20.

able electron affinity of the heterocyclic ring relative to the exocyclic oxygen atom and this situation might also give rise to susceptibility of the oxygen of the carbonyl group toward nucleophilic attack. Indeed, (67) reacts immediately with triphenylphosphine as does also the similarly electron-deficient 2,5-diphenyl-2,4-dicyanocyclopentadienone. In the latter case the crystalline adduct was obtained and characterized but in the case of (67), triphenylphosphine oxide and 4-hydroxy-3,5-diphenylpyrazol were isolated, which implies formation of (80) followed by hydrolysis on work-up.

It is well established that α -dicarbonyl azo compounds are three or four orders of magnitude more reactive than the corresponding olefins, and cyclic examples such as 4-phenyl-1,2,4-triazoline--3,5-diones are among the most active dienophiles known. Geometric factors and polarizability are certainly important, but the energetics of transforming an azo ester linkage into two C—N bonds and an unusually strong N—N bond may also be highly favorable. The literature on hydantoin chemistry indicated that several approaches which could have given 5-substituted dehydrohydantoins resulted instead in the formation of the *exo*-methylene tautomers (66BCJ1559). Two routes for the conversion of hydantoins to the corresponding dehydro form incapable of undergoing such an isomerization are oxidative dehydrogenation and substitution followed by elimination (70JOC3097).

On the other hand, a large number of 3,4-diaza-2,4-cyclopentadienone derivatives have been described. The earliest studies about these compounds were carried out by Freeman *et al.* (69JOC187, 69JOC194), who synthesized a series of substituted 3,4-diazacyclopentadienones, *N*-oxides and *N,N'*-dioxides. Treatment of β -aryl- α,β -unsaturated oximes with nitrous acid gave compound (**81**) because the 3,4-diaza-2,4-cyclopentadienone containing adjacent *N*-oxide functions was the only structure consistent with all the spectral data.

Reduction of ketone (**81**) with zinc and acetic acid produced the 4-hydroxypyrazoles (**87**), whereas reaction with dithionite gave the corresponding 1,4-dihydroxypyrazoles (**88**). These compounds could be oxidized with Fremy's salt (potassium nitrosodisulfonate) to the 3,4-diazacyclopentadienone 3-oxides.

Attempts were made to prepare the compound (**90**) using the method described above. However, nitrosation of either cinnamaldehyde or acrylophenone failed to give the desired product. In contrast, the tetraazafulvalene (**91**) was easily prepared (72CC961).

The low-temperature reduction of these compounds in THF with potassium metal leads to the formation of an anion radical solution yielding a simple ESR spectrum. The remarkable lack of temperature dependence of the hyperfine coupling constants for the entire series of anion radicals, the absence of alkali metal coupling, and the excellent agreement between the calculated and experimental spin densities would seem to indicate the lack of ion pairing in these systems. However, it is most likely that these anion radicals (**92**) are strongly ion-paired in THF. The fact that

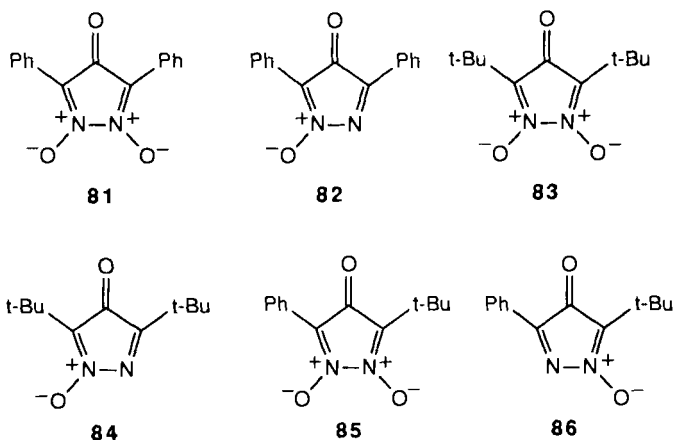


FIG. 21.

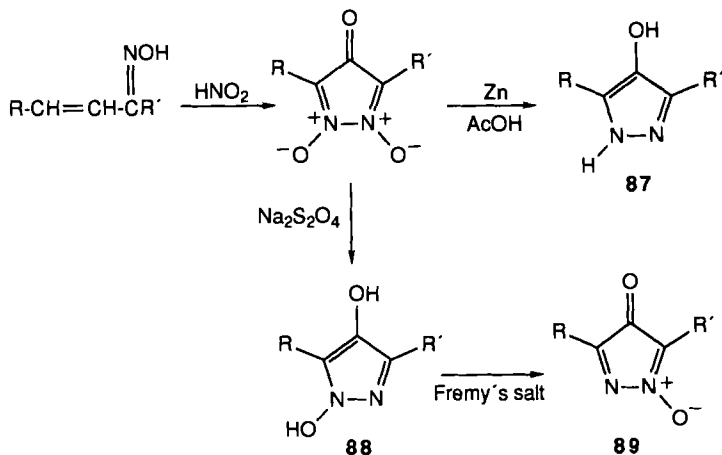


FIG. 22.

the addition of even small portions of HMPA (which reduces the amount of ion association) results in the immediate polymerization of the anion radical solution suggests that the thermal stability of the monomeric anion radicals is due to the tight ion association. Thus, the stability of the anion radical is dependent on the ion association, as the addition of very small amounts of HMPA to the THF solution causes a loss of the ESR signal and the formation of a visible precipitate. The lack of temperature-dependent coupling constants in the single ring systems is evidently due to the fact that the ion pair has a relatively rigid structure analogous to that shown in (93). For the *N*-oxide systems, the potassium cation is most probably sandwiched between the *N*-oxide oxygen and the unsubstituted nitrogen atom (79JOC3211).

The existence and reactivity of the parent compounds, 2,5-diaza-2,4-cyclopentadienone (94) and 3,4-diaza-2,4-cyclopentadienone (95), have also been demonstrated by using the three-phase test. Its reactivity as dienes and as dienophiles has been tested against several

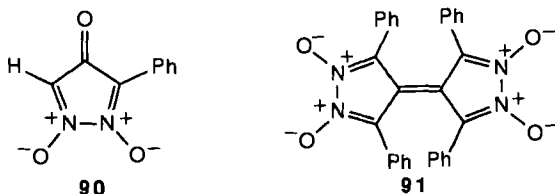


FIG. 23.

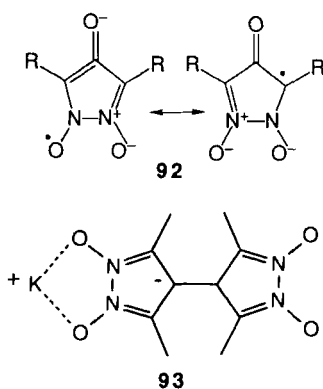


FIG. 24.

dienes and dienophiles trapping agents. The ability of 3,4-diaza-2,4-cyclopentadienone to react as a diene and as a dienophile was similar to that of 2,5-diphenyl-3,4-diaza-2,4-cyclopentadienone (78CJC904).

Lifetime determinations for these intermediates carried out with the Polyphasic Dynamic Reactor (90JOC2060) show that the position of the nitrogen atoms is more important than their actual number (Table II). Intermediate (**94**) has a very short lifetime. This seems to depend on the high reactivity of the *N*-acylimine group contained in their structures. Compounds (**40**) and (**94**) have a shorter lifetime than 3-aza-2,4-cyclopentadienone and (**95**); this could be due to the β -position of the nitrogen atom in these intermediates. The stability of (**41**) and (**52**) is similar to that of the homocyclic species, 2,4-cyclopentadienone. Intermediate (**63**) has a surprisingly long lifetime. This could be explained by taking into account that it has not reacted as a diene in Diels-Alder reaction.

When the intermediates were generated in the absence of a trapping agent, complex mixture in solution were always obtained. This behavior is also observed for the intermediates with just a nitrogen atom and several related carbocyclic intermediates.

C. HYDANTOIN DERIVATIVES

Treatment of the hydantoins (**98a-c**) with *t*-butyl hypochlorite in methanol gave the *N*-chloro compounds (**99**) in quantitative yield. Alcoholic solvents were required for the chlorination of (**98a**) and (**98b**), since there

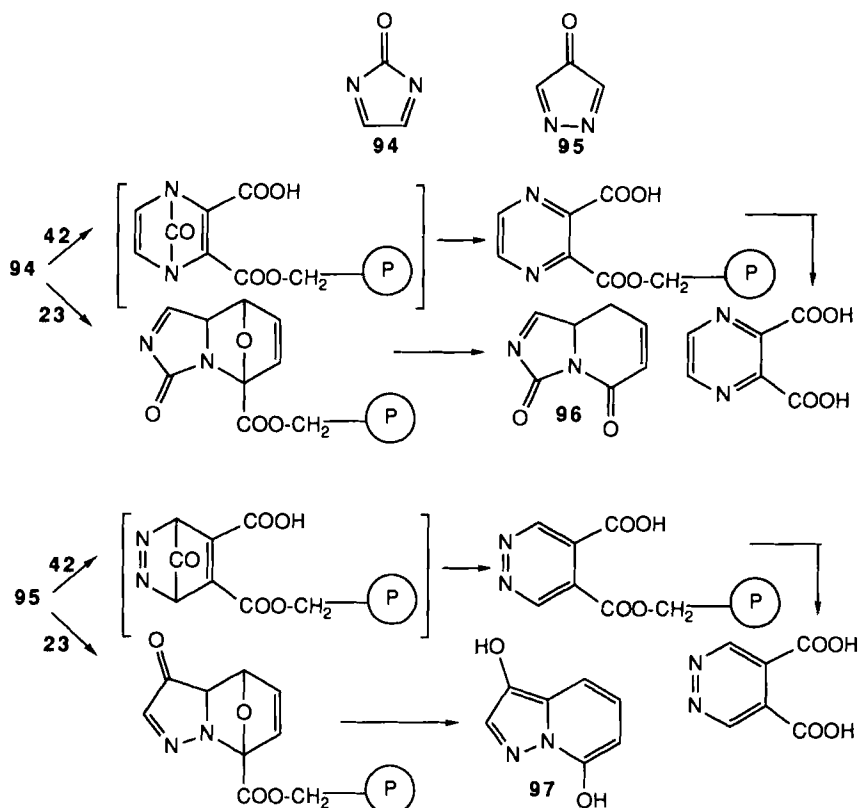


FIG. 25.

TABLE II
LIFETIME OF AZA- AND
DIAZA-2,4-CYCLOPENTADIENONES

Intermediate	Lifetime (s)
2-Aza-2,4-cyclopentadienone	2.0 ± 0.5
2,3-Diaza-2,4-cyclopentadienone	63.5 ± 0.5
3-Aza-2,4-cyclopentadienone	11.5 ± 0.5
2,5-Diaza-2,4-cyclopentadienone	1
3,4-Diaza-2,4-cyclopentadienone	16.0 ± 0.5

was no reaction in aprotic media; (**98c**) however reacted readily with *t*-butyl hypochlorite in acetonitrile.

Reaction of this *N*-chloro compound (**99a–c**) with triethylamine, tetramethylethylamine, or 1,5-diazabicyclo [5.4.0] undec-5-ene resulted in the elimination of hydrogen chloride and the formation of the dehydrohydantoin (**100a–c**). Evidence for the formation of the dehydrohydantoin was the precipitation of the amine hydrochlorite, the formation of 1,4-adducts with dienes and, in the case of (**99b**), the properties of the isolated products, (**100b**). All of the dehydrohydantoin are sensitive to moist air and are preferentially handled in an inert atmosphere.

5-Phenyl-3-methyldehydrohydantoin (**100b**) was isolated by sublimation; it is a crystalline, yellow compound, with substantial atmospheric stability, once purified. The dehydrohydantoin (**100c**) and (**100a**) could not be isolated because of their instability in the atmosphere; however, they could be generated and utilized *in situ*.

The dehydrohydantoin (**100a–c**) are active dienophiles and undergo [4 + 2] cycloadditions under mild conditions even with dienes of modest activity. The reactivity of the dehydrohydantoin depends markedly on the substituent in the 5 position with (**100c**) \gg (**100b**). The 5-phenyl compound (**100b**) reacted rapidly with cyclopentadiene and 1-methoxybutadiene and slowly with isoprene and cyclohexadiene at 25°C. There was no reaction with furan or 3,4-diphenyl-4,4-dimethylisopyrazole. Competitive experiments showed that it was substantially less reactive than *N*-phenylmaleimide with 2,3-dimethylbutadiene but that reactivity is probably greater than that of phenylmaleic anhydride. In contrast to (**100b**),

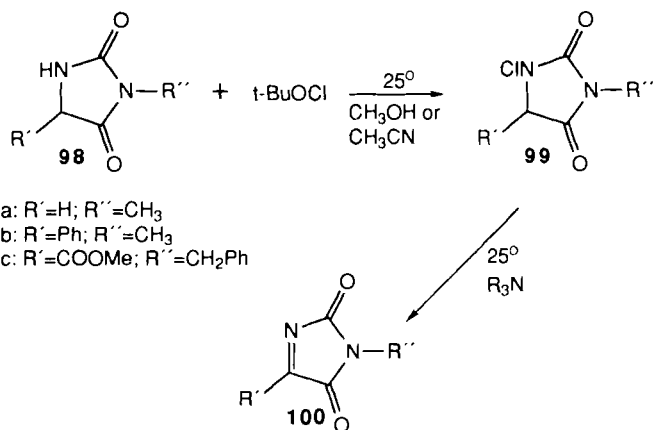


FIG. 26.

(100c) reacts within minutes with 1-methoxybutadiene, cyclohexadiene, or isoprene at 25°C. The parent dehydrohydantoin, (100a), undergoes side reactions under these conditions so that yields of cycloadducts are low and irreproducible, and rates of reactions are difficult to estimate.

The ambient stability of the dehydrohydantoins depends significantly on the substituent on the C=N bond. The 5-phenyl derivative (100b) is isolable, thermally stable, and easily handled, although it retains substantial reactivity in polar and cycloaddition reactions. The 5-carbomethoxyphenyldehydrohydantoin (100c) and the unsubstituted compound (100a) are progressively less stable. The observed trend in the stability of the dehydrohydantoins is in the direction expected from both steric and electronic considerations; bulky 5 substituents or those capable of conjugation should and do deactivate the imine linkage to attack by nucleophiles. The comparison of the ultraviolet spectrum of (100b) with those of similarly substituted maleimides shows the extent of interaction of the C=N with the carbonyls in the 2 and 4 positions and with 5 substituent.

It is of interest to comment on the position of the equilibrium between 5-alkyldehydrohydantoins and the 5-methylene (enamine) tautomers. The isolation of the 5-methylene isomers exclusively under what must have been equilibrating conditions indicates that the equilibrium lies very far to the right.

The fact that 5-alkyldehydrohydantoins should have limited atmosphere stability support this, since reaction of the 5-alkyldehydrohydantoin tautomer would lead to rapid deterioration of the sample. In most monounsaturated five-membered rings the isomer with the double bond exocyclic to the ring has substantial stability; however, in the hydantoin series the equilibrium lies far in this direction. The most important factors in driving this equilibrium toward the enamide are probably the energy gained by delocalization of the nonbonding electrons on the 1-N into the adjacent carbonyl and the formation of an N—H bond; this and the delocalization energy of the α,β -unsaturated amide must be large enough to counterbalance any benefit due to delocalization of the π -electrons in the cross-conjugated dehydrohydantoin.

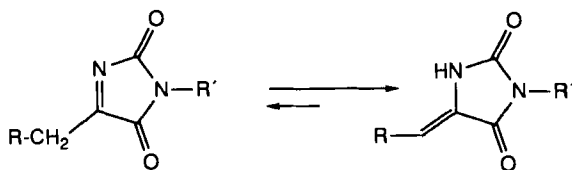


FIG. 27.

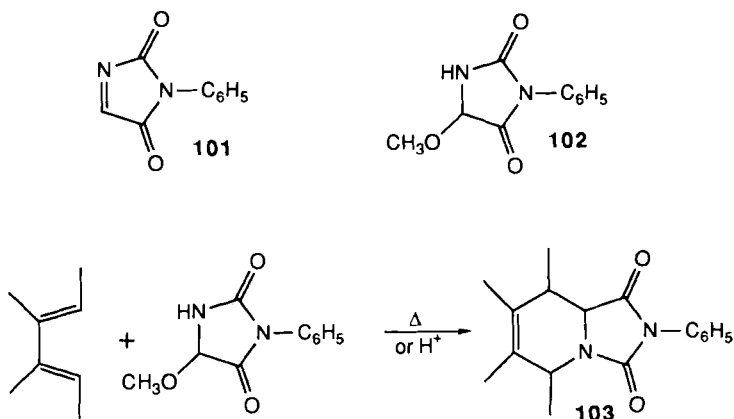


FIG. 28.

3-Substituted-5-methoxyhydantoin at 80°C with acids in the presence of the dienes affords satisfactory yields of Diels–Alder adduct. In certain cases products of carbonium ion reactions between the hydantoin and diene were also observed (69TL2631). One explanation for this behavior could be the free existence of (**101**) generated from (**102**).

Reacting butadiene, *trans*-piperylene, isoprene, 2,3-dimethylbutadiene, 2,4-hexadiene, 1,4-diphenylbutene, 1,2,3,4-tetramethyl butadiene, and 1,4-dimethyl-2,3-diethyl butadiene thermally with 3-phenyl, 3-*p*-chlorophenyl, and 3-benzyl-5-methoxyhydantoin gave Diels–Alder adducts in 16–80% yield. Reaction of 1,2,3,4-tetramethylbutadiene with 3-*p*-chlorophenyl-5-methoxyhydantoin gave a mixture of two adducts that according to their NMR spectra are a mixture of *cis*–*trans* isomers (**104**), (**105**) (71T3119).

The ratio of *cis* to *trans* isomers was found to depend on the nature of the diene and the reaction conditions. Thus, 2,4-hexadiene thermally gave only the *trans* isomer whereas the tetramethylbutadiene afforded, under

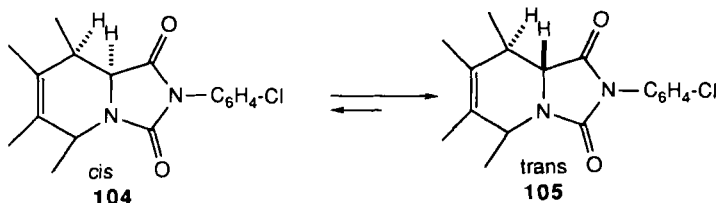


FIG. 29.

the same experimental conditions, a *cis-trans* ratio of 3 : 1. The ratio of isomers changed in favor of the *cis* isomers as the reaction temperature was lowered. The *cis* isomers were found to isomerize, thermally or in the presence of a base or acid catalyst, to the *trans* isomers. The *cis* adduct from 1,4-diphenylbutadiene was found to isomerize even on an alumina column.

The reactions of the methoxyhydantoin with dienes were found to be strongly acid-catalyzed. Thus, reacting 1,2,3,4-tetramethylbutadiene and 1,4-dimethyl-2,3-diethylbutadiene with 3-phenyl-5-methoxyhydantoin in boiling benzene and in the presence of β -naphthalenesulfonic acid afforded Diels-Alder adducts in 75 and 74% yield, respectively, and only the *cis* isomers were obtained. Under the same experimental conditions 1,1'-bicyclohexenyl afforded a mixture of *cis-trans* isomers in a 1 : 2 ratio and in a 76% yield. 2,4-Hexadiene, which reacted thermally with 3-*p*-chlorophenyl-5-methoxyhydantoin to give only the *trans* isomer in 53%, was found to react in boiling benzene and in the presence of trifluoroacetic acid to give only the *cis* isomer in 25% yield. This isomer isomerized to the *trans* isomer.

1,3-Cyclohexadiene reacted with the methoxyhydantoin in boiling benzene in the presence of trifluoroacetic acid to give the adducts (**106**) in 30–33% yield. The thermal reaction with *p*-chlorophenyl derivative gave (**106a**) in 75% yield.

These products are probably the *endo* isomers, since catalytic hydrogenation of the double bond of (**106b**) and (**106c**) to give compound (**107**) showed a deshielding effect on the phenyl group of (**106c**) and on the methylene and the phenyl of (**106b**) in the NMR spectra.

Although there was no big difference in yields between the thermal and the acid-catalyzed reaction with the tetra-substituted dienes, there was a

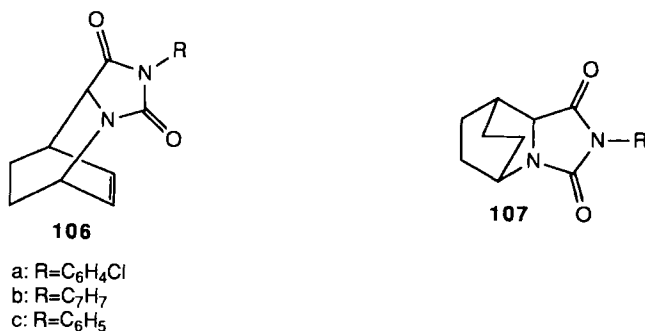


FIG. 30.

difference in yields with the di- and mono-substituted dienes. The acid-catalyzed reaction generally gave a more complex mixture of products with lower yields of the Diels–Alder adducts.

These results can be interpreted as being due to the reversible formation of the 3-substituted dehydrohydantoins by way of the 5-carbonium ions. Reaction of the dehydrohydantoins or the ions with dienes is slower than reaction with methanol but is irreversible. This system is useful for the preparation of certain cycloadducts of dehydrohydantoins. Its limitations result from the presence of methanol and acid, which preclude observation or isolation of the dehydrohydantoin and the utilization of most heteroatom-substituted dienes.

The dehydrohydantoins (**100a–c**) are reactive dienophiles even for (**100b**) in which the phenyl group affords a substantial steric hindrance to cycloaddition. The increase in activity obtained by incorporation of the imine moiety into a five-membered ring is consistent with results obtained with olefins and azo systems. Attempts to compare the activity of comparably substituted $C=C$, $C=N$, $N=N$ dienophiles are not wholly successful owing to the difficulty of evaluating the parent dehydrohydantoin system (**100a**). The 5-phenyl-3-methyldehydrohydantoin appears to be more reactive with isoprene than 3-phenylmaleimide anhydride by a factor of 5–10 and less reactive than *N*-phenylmaleimide by a similar amount. The 5-carboxymethyl-3-benzylhydantoin is substantially more reactive with isoprene and 1-methoxybutadiene than is maleic anhydride or *N*-phenylmaleimide and appears to be comparable in reactivity to an extremely active diene such as tricyanoethylene. The high reactivity of (**100c**)

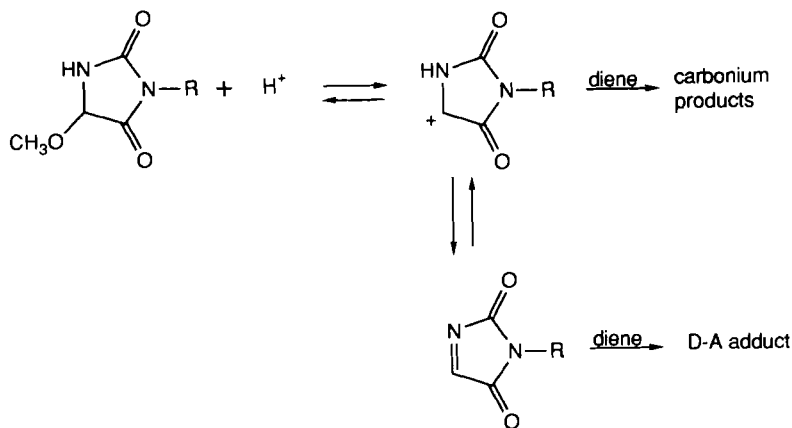


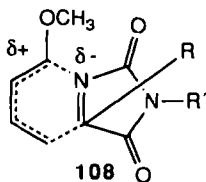
FIG. 31.

is, in part, accounted for by the presence of three electron-withdrawing substituents. Reaction of 1-methoxybutadiene with either (100a) or (100c) affords only the cycloadduct with the methoxyl group α to the nitrogen and probably *trans* to the phenyl or carbomethoxyl substituent. The observed regioselectivity has an analogy in the reports that 1-substituted butadiene reacts with monoacylethylenes to form primarily the 1,2-disubstituted cyclohex-3-enes. The explanation for the orientational selectivity in the carbocyclic systems is not known. In our reactions the preference is consistent with the contribution of polar structures to the transition state since charge delocalization is most favorable for (108). Other evidence indicates that the transition and ground states have similar polarities; however, the reactants used in these studies have dipoles and so a transition structure with some small amount of polar character is possible.

The characteristic features of the reaction between dehydrohydantoin and dienes are regioselectivity of products formation (in nearly all cases), the apparent absence of solvent effect, and the rate enhancement caused by electron-donating groups on the diene. These same phenomena are prominent in the concerted [4 + 2] cycloaddition of olefins to dienes, and the two reactions appear to have the same mechanism.

IV. Five-Membered Rings with More Than Two Nitrogen Atoms

4-Phenyl-1,2,4-triazoline-3,5-dione acts as a dienophile by *in situ* reaction with butadiene, cyclopentadiene, cycloheptatriene, and bicycloheptadiene (62TL615). Thus, it is possible to compare the reactivity of the *cis*-azo dienophile (110) with *trans*-azo dienophiles, such as ethyl azodicarboxylate, which has been observed to undergo alternate modes of reaction when used with less reactive or hindered dienes. Treatment of (110) with several dienes resulted in exclusively Diels–Alder addition. The results are summarized in Table III.



a: R=Ph; R'=CH₃
b: R=COOCH₃; R'=CH₂Ph

FIG. 32.

TABLE III
RESULTS OF THE DIELS-ALDER REACTION OF **110**
WITH SEVERAL DIENES

Diene	Adduct	Yield (%)
2,3-Dimethyl-1,3-butadiene	81	62
Isoprene	82	81
Piperylene	83	50
1,4-Diphenyl-1,3-butadiene	84	70
Cyclopentadiene	85	58
1,3-Cyclohexadiene	87	73
1,3-Cyclooctadiene	87	15
Anthracene	88	46
Bicycloheptadiene	89	27

A reaction that deserves special comment is the reaction of (**110**) with cyclopentadiene. The resultant adduct was reported but no mention was made of the melting point or points. The possibility of formation of *exo* and *endo* isomers exists. Both isomers may be formed, a priori, or one isomer might be converted to the other without bond breaking, although inversion of both nitrogen atoms would be necessary. This inversion is not possible for its carbon analog, i.e., the *N*-phenylmaleimide adduct of cyclopentadiene. In the case of (**115**), it might be expected that the conversion of *endo* to *exo* would have a higher barrier to inversion than the 19 kcal/mol reported for 1,2-dicarbomethoxy-3,6-diphenyl-1,2,3,6-tetrahydropyridazine (65CC426).

In general, reaction of (**110**) with a wide variety of dienes was quite satisfactory (67JOC330). Only the most unreactive dienes such as hexachlorocyclopentadiene and hexachlorobutadiene failed to react under the conditions employed. The chief limitation of this dienophile is that the mixture cannot be heated to force reaction without the decomposition of (**110**). Another important observation was the strong, almost complete preference for undergoing the Diels-Alder-type addition even when other reactions are possible. This may be attributed to the two favorable factors of *cis* configuration and electron deficiency that are exhibited by 4-phenyl-1,2,4-triazoline-3,5-dione.

The strong reactivity of this compound has been employed in the synthesis of triazasteroids with the nitrogen atoms situated in different positions (77TL4141). Thus, reaction of the 1,2,3-triazolin-3,5-dione (obtained by *t*-butyl-hypochlorite oxidation of the 1,2,4-triazolidine-3,5-diones) with diverse 1-vinyl-hydronaphthalene derivatives gave the expected adducts,

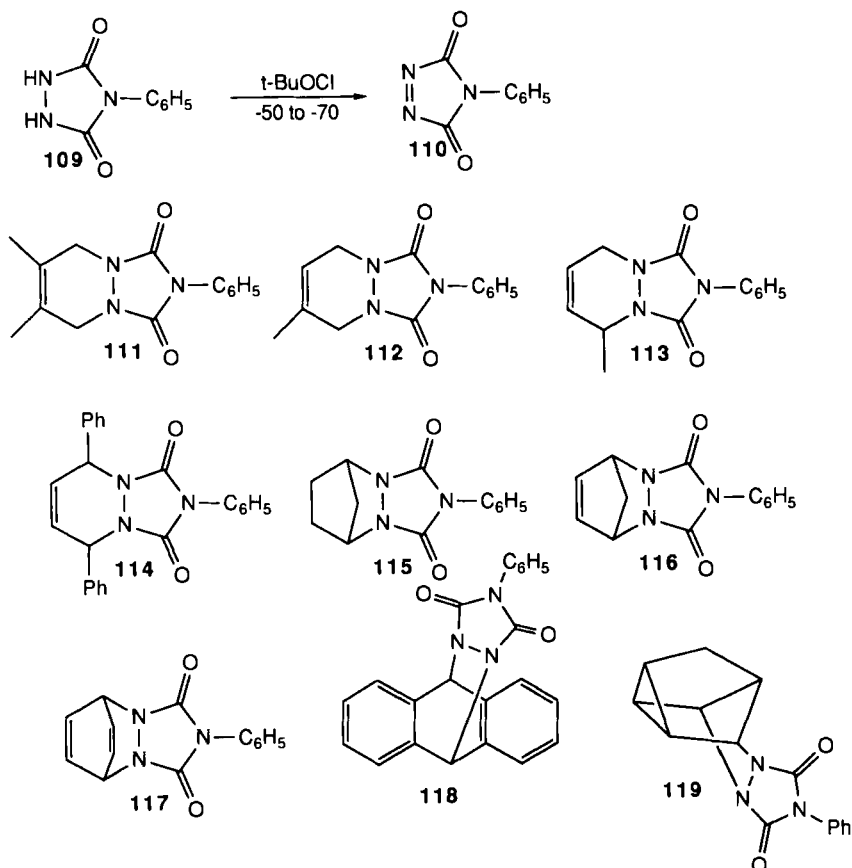


FIG. 33.

which by hydrogenation yield the 13,14,16-triazasteroids (**120**), (**121**), (**122**), (**123**).

V. Six-Membered Rings with One Nitrogen Atom

The nitrogen heterocyclic analogs of quinones, azaquinones, are interesting heterocyclic compounds, but have received only limited attention. In fact, 2-aza-3-phenyl-1,4-naphthoquinone is one of the first examples in the literature (69HCA1810; 71TL1621). There are several examples of other hydroxylated derivatives that can exist in several tautomeric forms, and no evidence has been presented that unambiguously establishes which

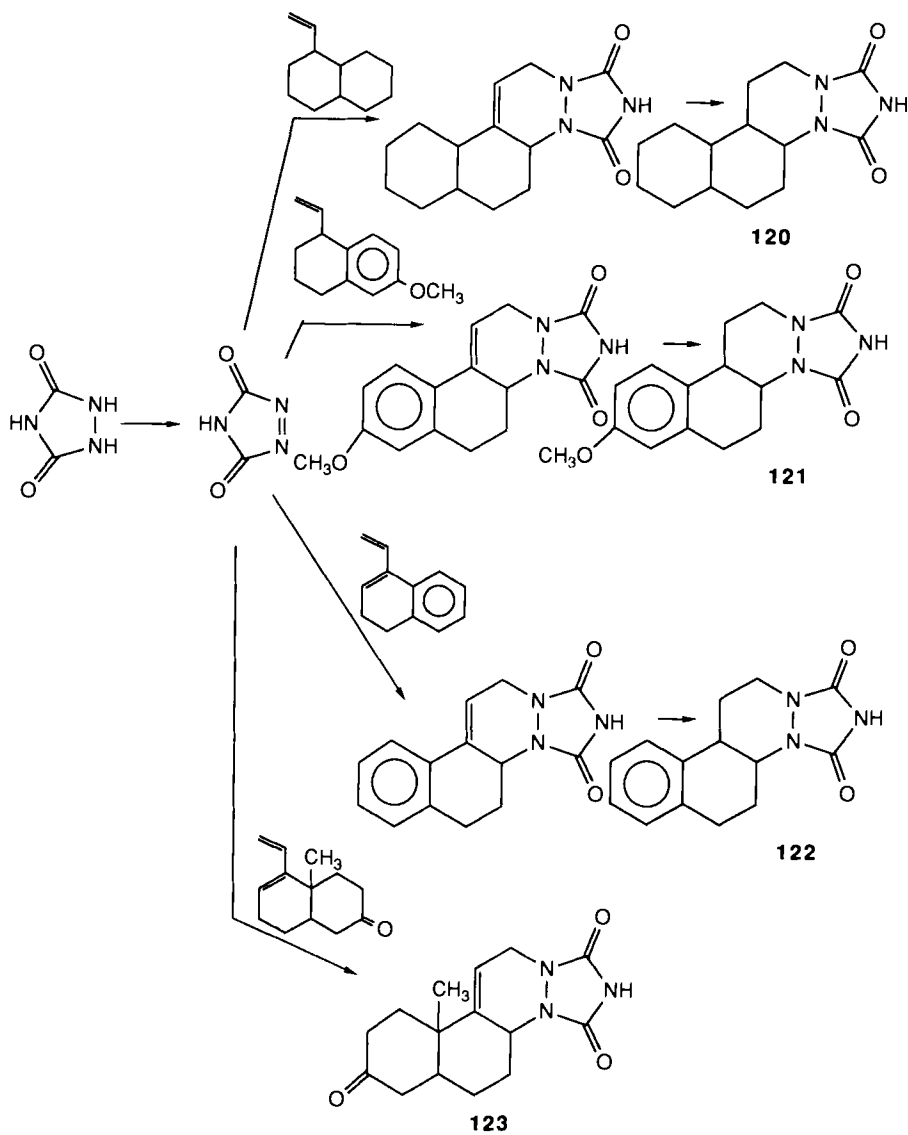


FIG. 34.

isomer or isomers predominate. The paucity of chemical information relating to azaquinones is undoubtedly due to a lack of viable synthetic routes to such compounds. The oxidation of the aminopyridones (**124**) and (**125**) or 3-hydroxy-2-pyridone with manganese dioxide, chromium trioxide, or potassium bromate results in hydroxylation of the unsubstituted α -position and formation of the corresponding tautomeric hydroxyazaquinones (**126**), which were isolated as quinhydrone (57JA3552). When the isoquinoline derivative (**127**) was subjected to thermolysis at 170°C, a good yield of 2-aza-3-phenyl-1,4-naphthoquinone (**128**) was observed (69HCA1810). This same azaquinone was obtained as a major product upon thermal decomposition of 2-azido-2-phenyl-1,3-indandione (**129**) in refluxing decalin (71TL1621). In addition 2,2-diazido-1,3-indandione (**130**) thermally rearranged in refluxing toluene to the tetrazole (**131**) in 94% isolated yields and 2-aza-3-azido-1,4-naphthoquinone has been proposed as its precursor.

The observed ring expansion of 2-azido-2-phenylindandione (**129**) and 2,2-diazido-1,3-indandione (**130**), along with the established propensity of 2,6-diazido- and 2,5-diazido-1,4-quinones to undergo easy, thermally induced ring contractions to 2-cyano-4-azido-1,3-cyclopentene-diones suggested a unique synthetic route to 2-aza-3-cyano-1,4-quinones (75JA6181).

Thermolysis of 2,3-diazido-1,4-naphthoquinone (**132**) in refluxing *o*-dichloroquinone was studied, and *o*-phthaloyl cyanide (**133**) (40%) and 2-aza-3-cyano-1,4-naphthoquinone (**135**) (20%) were isolated. The above yields are limits as evidenced by the fact these compounds could be trapped *in situ* to give adducts in higher yields based upon the starting diazide. For example, addition of *trans, trans*-2,4-hexadiene followed by anhydrous methanol to the reaction solution after it was cooled to ambient temperature gave the Diels–Alder adduct (**136a**) (38%) and 3-cyano-3-methoxyphthalide (**48**). In separate experiments, the cycloaddition of the azaquinone to the diene was found to give (**136a**), in nearly quantitative yield, and the reaction of *o*-phthaloyl cyanide with methanol gave an 80% yield of the phthalide.

Another precursor to the azaquinone (**135**), 2-azido-2-cyano-1,3-indandione (**134**), was isolated in 18% yield when 2,3-diazido-1,4-naphthoquinone was decomposed in chlorobenzene at 95–100°C. Under these conditions, a 61% yield of *o*-phthaloyl cyanide was also realized, and no azaquinone was detected. Subsequent thermolysis of (**134**) in refluxing *o*-dichlorobenzene gave the azaquinone (**135**) in 75% isolated yield.

In an analogous fashion, the thermal chemistry of 2,3-diazido-5-*tert*-butyl- (**137**) and 2,3-diazido-5-phenyl-1,4-benzoquinone (**138**) has been investigated. When the thermolysis of these compounds was carried out in refluxing *o*-dichlorobenzene, the *tert*-butyl substituent analog gave nearly

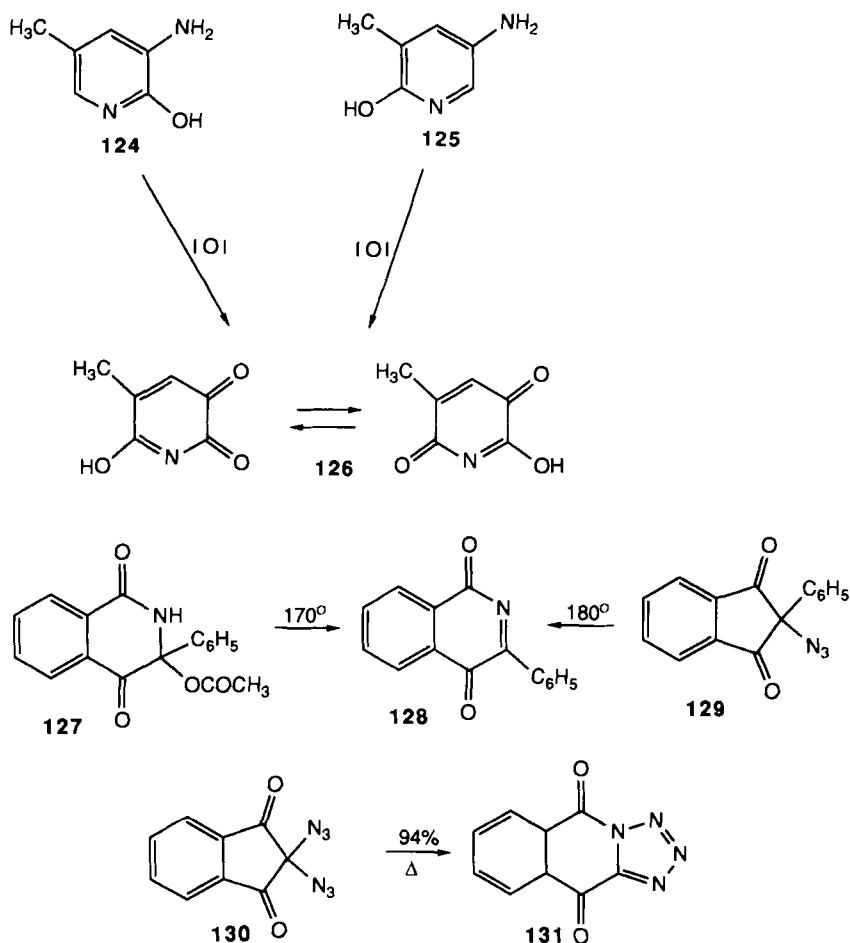


FIG. 35.

equal amounts of the isomeric azaquinones (**139**) and (**140**) in overall 55% isolated yield. 2,3-Diazido-5-phenyl-1,4-benzoquinone (**138**) also gave a mixture of isomeric azaquinones (**143**) and (**144**), which were isolated as their Diels-Alder adducts to *trans, trans*-2,4-hexadiene, respectively, 6-cyano-7,10-dimethyl-4-phenyl (**145**) (11%), and 6-cyano-7,10-dimethyl-3-phenyl-1-azbicyclo [4.4.0] deca-3,7-diene-2,5-dione (**146**) (9%).

It is thus clear that thermal rearrangements of 2,3-diazido-1,4-quinones proceed in two discrete stages. The first involves the formation of the diacyl cyanides and 2-azido-2-cyano-1,3-cyclopentenediones; the second entails the subsequent ring expansion of these cyclic azides to 2-aza-3-

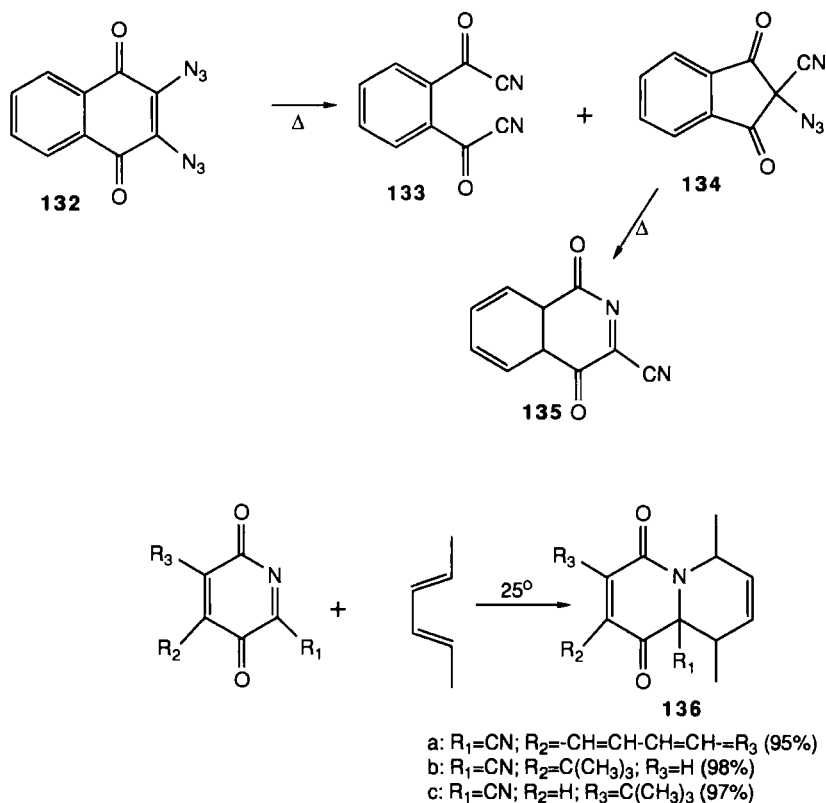


FIG. 36.

cyano-1,4-quinones. The formation of the 2-azido-2-cyano-1,3-cyclic diones in the initial stages, in essence, a further example of the thermal rearrangement of 2-azido-2-substituted 1,4-quinones to 2-cyano-2-substituted 1,3-cyclopentene diones, and the mechanism of this transformation have been reported (73JA2603).

This rearrangement proceeds by collapse of the azidoquinone (147) to the azirine (148) followed by ring opening to the zwitterion (148), which undergoes C-acylation to the cyclic dione (151). The mode of formation of diacyl cyanides is not apparent. A nitrene mechanism is not attractive since the 2,3-diazo-1,4-quinones decompose at 80–90°C, whereas organic azides which lead to nitrenes in the rate-determining step require temperatures in the range 140–170°C. A mechanism involving the formation of a diazene intermediate in the rate-limiting step is also untenable on the bases of existing kinetic data.

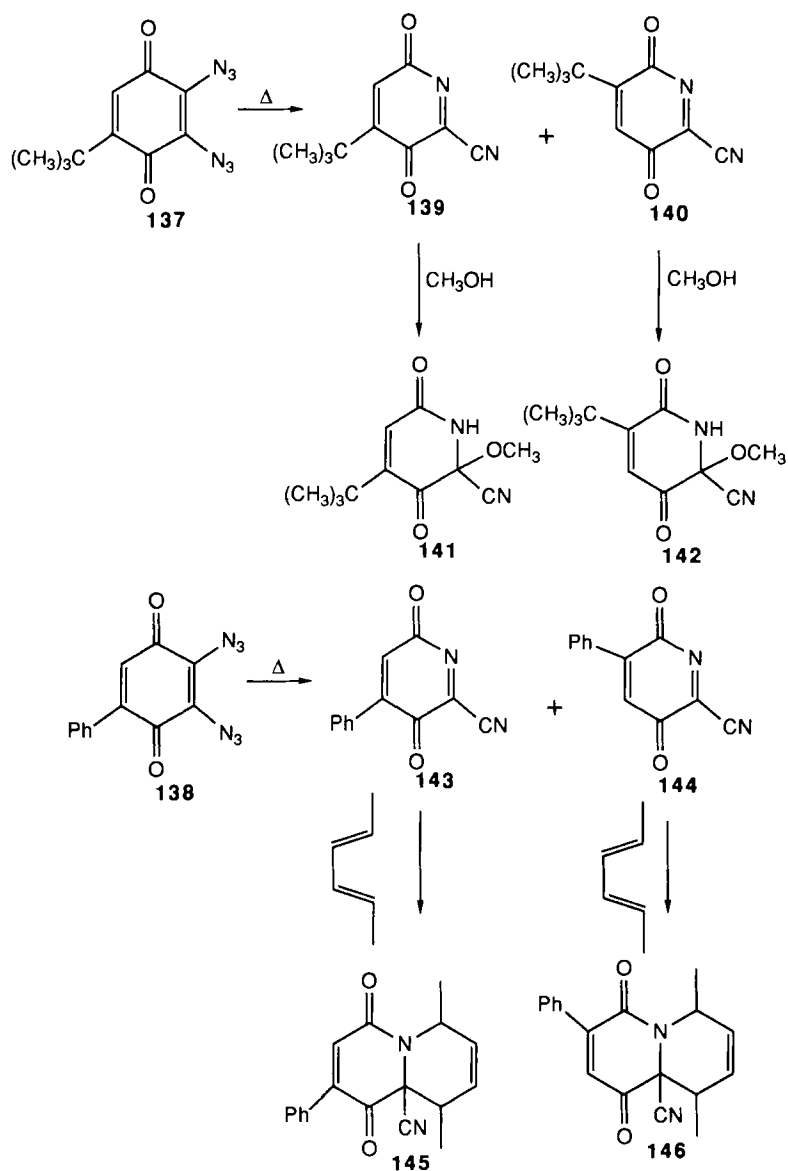


FIG. 37.

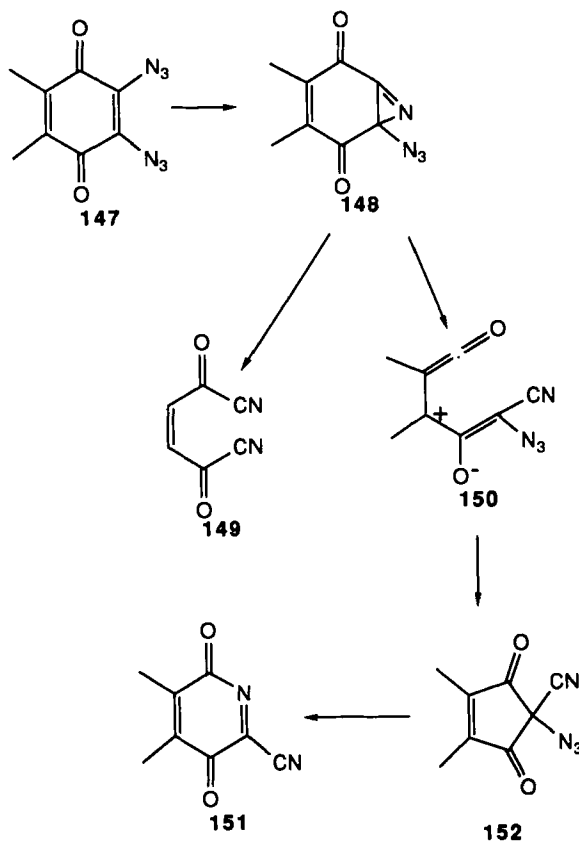


FIG. 38.

The chemistry of azaquinones centers around the electron-deficient imine double bond. For example, water, methanol, ammonia, methylamine, nitromethane, *m*-xylene, and enamines all add readily to the imine double bond in aza-3-phenyl-1,4-naphthoquinone. On the other hand azaquinones are also potent dienophiles and thus can function as starting materials for a large variety of highly substituted new heterocyclic compounds.

VI. Six-Membered Rings with Two Nitrogen Atoms

The oxidation of diacyl hydrazides with lead tetraacetate is a convenient method for the preparation of diacyl diimides, generally superior to the methods usually employed (56JA335; 90JHC1741). However, when the

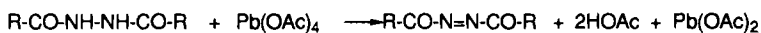


FIG. 39.

reaction was applied to 2,3-dihydrophthalazine-1,4-dione, the expected product, phthalaizine-1,4-dione, was not isolated. Contrary to the behavior of other diacylhydrazides, gas was evolved during the oxidation and the initially highly colored solution became quite colorless during the isolation procedure.

Examination of the reaction of (153) with lead tetraacetate provides evidence that the initial product of oxidation is indeed the expected diimide, which is too unstable to be isolated or even to be preserved in solution. When the oxidation of 2,3-dihydrophthalazine-1,4-dione with 1 mol of lead tetraacetate was carried out, a lime-green solution was initially obtained that very rapidly deposited a fine, white, amorphous solid and that became colorless in the course of a few hours. The amorphous solid was an intractable substance that decomposed (usually explosively) when heated. This material is composed, in roughly equivalent amounts, of phthalic anhydride and unchanged initial product. So, it seems that oxidation of (153) was proceeding, simultaneously, according to Eq. (1) and (2); that (154) was responsible for the color of the solution; and that because of its instability, (154) was being removed rather rapidly according to Eq. (4) to form a polymer (60JOC1724).

Intermediate (154) has been intercepted by using butadiene as a trapping agent. In fact when butadiene was added to the clear green solution, the green color disappeared immediately and 1,4-dihydro-pyridazino[1,2-*b*]phthalazine-6,11-dione (155) was produced in an amount roughly equivalent to that of the polymer product formed from the green solution in the absence of butadiene; the amounts of unchanged (153) and phthalic anhydride obtained in the two experiments were also roughly equivalent. These observations indicated that (155) and the polymer product were derived from an identical precursor, which most likely was (154) and which was responsible for the green color.

When the oxidation was carried out with butadiene present from the start, (155) was obtained in a 90% yield. This result showed that the initial product of oxidation is (154) as defined by Eq. (1). Because of its instability, however, (154) disappears according to Eq. (3) and (4), reaction by the latter route consuming additional oxidant and, with a molar amount of oxidant, requiring 1 mol of (153) to remain unchanged for each mole of anhydride produced. The reactivity of (154) as a dienophile, however, is greater than its reactivities according to Eq. (3) and (4), and in the presence of butadiene, (154) is intercepted by it essentially as rapidly as it is formed.

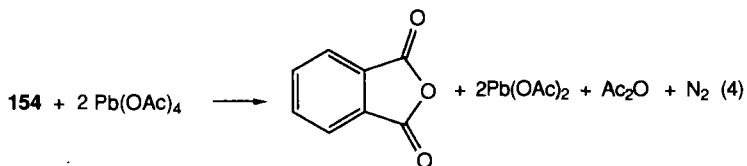
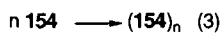
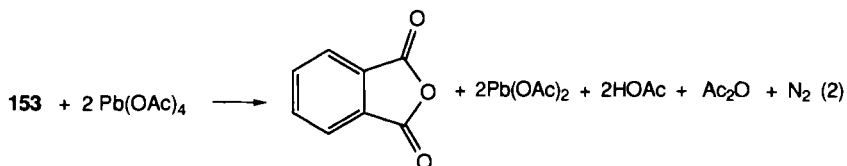
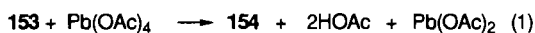
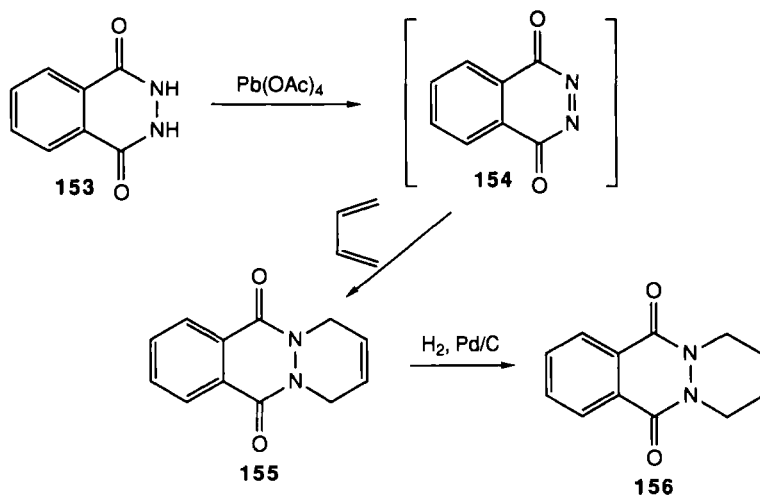


FIG. 40.

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The Nitration of Phenyl-Substituted Heterocycles

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I. Introduction

A. BACKGROUND

Since the early days of organic chemistry, nitration has been considered to be an important reaction and has been widely used. As early as 1825 Faraday discovered benzene and recorded its reaction with nitric acid. Shortly after, the use of nitric acid : sulfuric acid mixtures to effect nitration was reported and was soon quoted in a patent. Nitration figured prominently in the development of ideas of theoretical organic chemistry in the early part of the twentieth century and, as the most widely applicable and most widely used example of electrophilic substitution, it played an important role in the consideration of aromatic stability and reactivity. In 1910 the first report of orientation and deactivation in aromatic electrophilic substitution was published (10M11).

During the 1920s Ingold, Robinson, and others carried out extensive studies on aromatic electrophilic substitution, whereas in more recent years the work of Schofield, Ridd, Katritzky, and their co-workers have contributed so much to the body of data and to the understanding of aromatic electrophilic substitution, especially nitration.

This review was originally intended to cover electrophilic substitution in phenyl-substituted heterocycles in general. However, it was decided to concentrate on nitration since this provides the substantial majority of studies in this area. It is the only reaction that seems to have been systematically investigated to any extent and is the only reaction for which there are data for a wide range of phenyl-substituted heterocycles. The literature has been searched to 1991. However, few references have been found in the last 5 years.

Nitration is widely applicable, can be carried out under a variety of conditions, can usually be stopped cleanly after mononitration, is usually effected by the nitronium ion, can take place on a neutral molecule or a cation, and in many cases can be considered as the standard aromatic electrophilic substitution. However, this last point must be treated with caution. Depending on the reaction conditions and reagents, the mechanism of the reaction does vary, and accompanying reactions such as oxidation (due to the oxidative action of nitric acid), acetoxylation (by acetyl nitrate), and migration of nitro groups following ipso attack (80M11) can occur. Ipso nitration processes have been extensively studied by Fischer and co-workers.

Schofield (80M11) has provided a comprehensive review of aromatic nitration but with slight emphasis on phenyl heterocycles. There have also been extensive reviews of the methods and mechanisms of nitration

covering the literature up to 1988 (82PNA4487; 89MI1, 89MI2). The intention of this review is to summarize the results of the nitration of phenyl-substituted heterocycles and, by bringing this information together, to attempt to correlate and to rationalize the results.

This review is organized into sections according to ring size, number of heteroatoms, and fused ring systems. Systems with fused benzo rings are mentioned together with the parent heterocyclic ring. Any ring that does not fit the standard pattern is considered separately under Miscellaneous Systems. Where there are two (or more) fused heterocyclic rings, the compound is covered in the section relating to the principal heterocycle. Finally, where appropriate, details of the nitration of benzyl- or other phenyl-containing substituents are included, and other electrophilic substitutions are given if they are of interest.

B. NITRATION METHODS AND METHODS OF STUDY

There are many methods for effecting the nitration of aromatic compounds. Reactive compounds, for example, phenol, will nitrate in dilute nitric acid, but usually more vigorous reaction conditions consisting of nitric acid (either concentrated or fuming) or nitrate salts in sulfuric acid are used. Solutions of nitric acid in other mineral acids, e.g., perchloric or phosphoric acid, have sometimes been used and can give nitro products in isomeric proportions different from those found in sulfuric acid solution. Nitric acid in organic solvents, particularly acetic acid or acetic anhydride, has also been used frequently. In acetic anhydride acetyl nitrate rather than the nitronium ion is usually the reacting species.

Several competing reactions are observed. For example, oxidation by nitric acid, and sulfonation by sulfuric acid, can occur, particularly at elevated temperatures. Acetoxylation can also accompany nitration, and adducts may be formed in nitric acid : sulfuric acid ("mixed acid") mixtures as well as in nitric acid : acetic anhydride (60JCS4885; 64JA1067; 72JA7921; 73JA6128; 74JA4335). Nitro group migration may occur by addition of the nitronium ion to the site bearing a substituent followed by intramolecular rearrangement to the *ortho* position [71JCS(B)2443], an explanation for the high *ortho* : *para* ratios accompanying some nitrations using nitric acid : acetic anhydride. These "ipso" nitration processes have now been studied extensively.

Although nitration has been studied for many years, little systematic work seems to have been carried out in the area of phenyl-substituted heterocycles. There has been a report, "Nitration of Phenyl Substituents of Heterocyclic Nuclei" (30JCS397) but this only describes a few examples

of phenylimidazoles. "The Nitration of Some Phenyl Substituted N-Heterocycles" (88H371) also give just a few examples. However, Katritzky and co-workers have started an extensive study of the nitration of heteroaromatic species and have discussed the standardization of rates [75JCS(P2)1609] and have given a theoretical treatment of electrophilic substitutions in *N*-phenyl heterocycles (86H2545).

Belenkii has reviewed the effect of acid-base properties of heteroaromatic compounds on their electrophilic substitution reactions (86CHE587).

II. Five-Membered Ring Systems and Their Benzo Derivatives

A. SINGLE HETEROATOM SYSTEMS

1. Pyrroles

Pyrrole and its derivatives have been extensively studied. General references include Jones and Bean (77M11), Boyer (86M11), and Schofield (67M11). However, there are few reports of nitrations of pyrrolines and pyrrolidines.

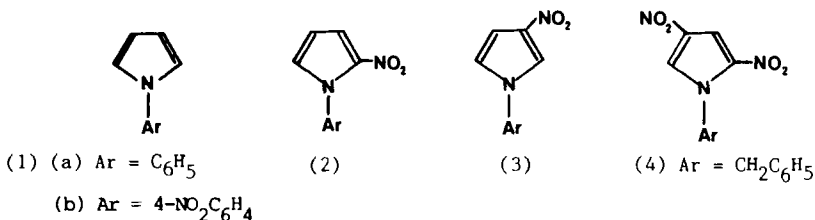
Pyrrole is a " π -electron excessive" compound and reacts at the 2-position with electrophiles more rapidly than benzene. However, depending on the acid strength, either the free base or the conjugate acid is the reacting species.

The nitration of 1-phenylpyrrole (**1a**) using nitric acid in sulfuric acid gives 1-(4-nitrophenyl)pyrrole (**1b**, 25%) as the only product (43RTC177). Under these conditions, the predominant specie is the conjugate acid, the presumed reactant, so nitration occurs in the phenyl ring. Nitric acid in acetic anhydride at -10°C gives the 2- and 3- nitro isomers (**2,3**) with no phenyl ring substitution, the 2:3 isomer ratio being 2:1 (66% yield) (43RTC177). However, the nitration of 1-phenylpyrrolidine in acetic acid at -20°C using nitric acid (*d* 1.35) gives 1-(4-nitrophenyl)pyrrolidine (52%). Bromination in acetic acid at 15°C also leads to 4-bromination in the phenyl ring (90%) (51IZV166).

The nitration of 1-benzylpyrrole in acetic anhydride at -10°C also gives the 2- and 3-isomers in the ratio 0.7:1 (62%) 67CJC2227). In another study 1-benzylpyrrole gives the same 2- and 3-nitro isomers in the ratio 0.67:1 (70%) (70M11).

If the initial molar ratio of nitric acid is 2:1, the yield of 3-nitro-1-benzylpyrrole is diminished and 1-benzyl-2,4-dinitropyrrole (**4**, 15%) is also obtained. Nitration of either the 2- or the 3-mononitro isomer gives

this same dinitro product, but further nitration using nitric acid either in acetic anhydride or in sulfuric acid at 0°C is unsuccessful (70MI1).



The nitration of 1-(4-nitrophenyl)pyrrole using nitric acid in acetic anhydride also gives 2- and 3-nitro products (**2b,3b**) in the ratio 1.43 : 1 (34%), whereas such a nitration using 1-(2-nitrophenyl)pyrrole gives the 2- and 3-nitro products in the ratio 1.07 : 1 (53%) (79JOC2321). The further nitration of 3-nitro-1-(x-nitrophenyl)pyrroles, using nitric acid in sulfuric acid, gives the results shown in Table I.

The nitration of 2-methyl-5-phenylpyrrole yields predominantly the 3-nitro derivative (**5a**). Other electrophiles also react at the 3-position to form products (**5b,c,d**) [73AC(R)245].

The nitrosation of 2-methyl-5-phenylpyrrole yields the 3-nitroso derivative predominantly (60%) together with the 4-nitroso product (30%) [71AC(R)237].

Some polyphenylpyrroles (**6a-d**) form 3-nitro derivatives (with some 3,4-dinitro products) when nitrated with nitric acid in acetic acid [56AC(R)263,56G95; 60AC(R)237; 66AC(R)866; 72AJC2687].

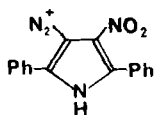
The nitration of 2,5-diphenyl-3-phenacysulfonylpyrrole (**7**) and of 2,5-di-phenyl-3-pyrrol-3,5-dimethyl(and diphenyl)-4-isoxazolyketone (**8**), using nitric acid:acetic anhydride, results in the formation of the 4-nitro products, the yields being 65,75, and 85%, respectively (76JHC645).

The nitration of 1,2,3,5-tetraphenylpyrrole, using nitric acid:acetic acid, gives the 4-nitro derivative (66MI1) as does 1-methyl-2,5-diphenyl-3-(2-pyridyl)pyrrole (**9**). The action of fuming nitric acid at 0°C on ethyl

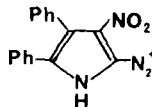
TABLE I
NITRATION PRODUCTS (HNO₃:H₂SO₄) OF 3-NITRO-1-(X-NITROPHENYL)PYRROLES
(79JOC2321)

	2,4-Dinitro	3,4-Dinitro	2,3,4-Trinitro
1-(4-Nitrophenyl)-3-nitropyrrole	75	15	10
1-(2-Nitrophenyl)-3-nitropyrrole	72	28	—

(60JCS3270). A similar reaction using excess nitrous acid and a prolonged reaction time converts 2,4-diphenylpyrrole to 5-diazonio-2,4-diphenyl-4-nitropyrrole (**13**) (62JCS1638).



(12)



(13)

The reaction of 3-acyl-2,5-diarylpyrroles with alkyl nitrites produces the corresponding 4-nitrosopyrroles without complications (56G1059; 62MI1; 64MI1).

Nitrations of 2,5-diphenyl and 2,4,5-triphenylpyrrole using amyl nitrite in ether give the 3-nitro product (39G315).

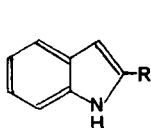
The nitration of α -ethyl- α -phenylglutarimide using mixed acid at -100°C was first reported to form mainly the 4-nitrophenyl product, with some *ortho* nitration. But in the case of the α -methyl analogue, no *ortho* product was seen [58CI(L)69]. More recently the nitration of the ethyl-phenyl compound has been shown to give 99% of the 4-nitrophenyl product (89EGP272771).

2. Benzopyrroles

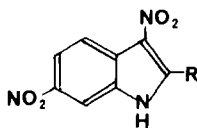
For a general review of the indoles, including a theoretical treatment of indole reactivity and substituent effects, see Sundberg (70MI2).

The nitration of indole (**14a**) in acetic anhydride occurs in both the pyrrole and the benzene rings to produce 3,6-dinitroindole (**15**), whereas in sulfuric acid, in which the conjugate acid is the reactant, nitration occurs to yield 5-nitroindole (16) (63JOC2262; 64TL803).

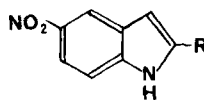
The nitration of 2-phenylindole in acetic acid also produces the 3,6-dinitro derivative (40%), whereas nitration using the nitrate salt in sulfuric acid gives the 5-nitro product (87%) (66JOC65).



(14) (a) R=H
(b) R=Ph

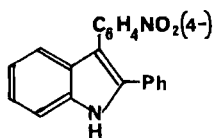


(15) R=H

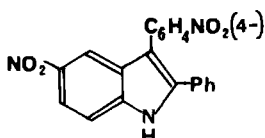


(16) R=H

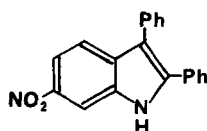
The nitration of 2,3-diphenylindole using potassium nitrate in sulfuric acid at 0°C (24 h) gives 3-(4-nitrophenyl)-2-phenylindole (**17**, 6%) and 5-nitro-3-(4-nitrophenyl)-2-phenylindole (**18**, 17%) with no trace of 6-nitro-2,3-diphenylindole (**19**) (65T823). However, the nitration of 2,3-diphenylindole using copper(II) nitrate in acetic acid at 100°C (10 min) gives 6-nitro-2,3-diphenylindole (21%), this same product also being obtained by nitration using nitric acid in acetic acid (58JCS1).



(17)



(18)



(19)

Nitration of 2-methyl-3-phenylindole using potassium nitrate in sulfuric acid also yields a mixture of 2-methyl-3-(4-nitrophenyl)indole (13%) and 2-methyl-5-nitro-3-(4-nitrophenyl)indole (2%). This dinitro product is also obtained by a second nitration of the mononitro compound. However, nitration of 3-methyl-2-phenylindole under these conditions gives only the 5-nitro derivative (80%) with no nitration in the phenyl ring.

These results indicate that, in acetic acid solution in which indole is unprotonated, the 3-phenyl ring is less reactive than the indole benzo ring, but that in sulfuric acid in which indole is protonated, the 3-phenyl ring is more reactive and the heterocyclic system is *para* directing. Even in sulfuric acid the 2-phenyl ring is less reactive than the benzene ring of indole (cf. protonated benzylidene aniline, Fig. 2) (66JOC65).

3-Nitro-2-phenylindoles are obtained by electrophilic ipso-nitration of arylazo, hydroxymethyl, and acyl groups on treatment with two equivalents of 70% nitric acid in acetic acid at 25°C. No attack on the phenyl ring is observed under these conditions [80MI1; 81JCS(P2)628]. Indolenines undergo nitration mainly at the 5-position (77-85%) (64TL803).

The nitration of 2-phenylindolizine seems to be critically dependent on the reagents and the reaction conditions. The addition of one equivalent of nitric acid at 0°C gives 2-(4-nitrophenyl)indolizine (41%) and a small

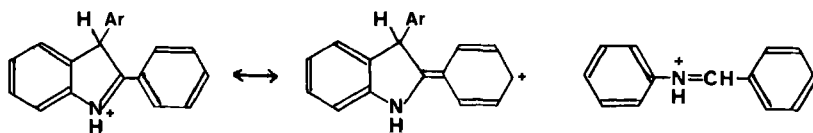


FIG. 2.

amount of 1-nitro-2-(4-nitrophenyl)indolizine. However, warming 2-phenylindolizine in nitric acid (*d* 1.4) produces 1,3-dinitro-2-phenyl indolizine (14%) (46JCS1077). Similar results have been obtained by Lins and co-workers (82JPS556). 2-Phenylindolizine also iodinate to give the 1,3-diiodo product (71MI1).

Kinetic and mechanistic studies have been carried out on 2-phenylindolizine and 1-methyl-2-phenylindolizine [79JCS(P2)312]. However, the studies on 2-phenylindolizine (using a twofold excess of nitric acid in sulfuric acid) indicate a more complex product composition than that reported in the earlier literature (46JCS1077) and, in addition to the 2-(4-nitrophenyl) and 1-nitro-2-(4-nitro-phenyl) derivatives, about 20% of a third product, believed to be the 3-nitro-2-(4-nitrophenyl) product, is obtained. However, the identity of this product does not seem to have been confirmed.

Nitration of 1-methyl-2-phenylindolizine gives 90% of the 1-methyl-2-(4-nitrophenyl) product under these conditions, and the results indicate that nitration occurs on the conjugate acid of the indolizine resulting from protonation at C-3 [69JCS(C)1279] (Fig. 3).

The nitration of 1-methyl-2-phenylindolizine in acetic anhydride at 5°C (3 h) gives 1-methyl-3-nitro-2-phenylindolizine (33%). On nitrosation both 2-phenyl- and 1-methyl-2-phenylindolizine give the 3-nitroso product in sulfuric acid. The neutral molecule appears to be the reacting species [46JCS1075; 69JCS(C)1279] Nitrosation of 1,3-diphenylindolizine also gives the 3-nitroso derivative (96%) [72JCS(P1)2974].

Nitration of 3-acetyl-2-phenylindolizine using nitric acid in sulfuric acid gives a mixture of 3-acetyl-2-(4-nitrophenyl), 3-acetyl-1-nitro-2-(4-nitrophenyl), 3-nitro-2-(4-nitrophenyl), and 1,3-dinitro-2-(4-nitrophenyl) indolizine (Fig. 4) (46JCS1077).

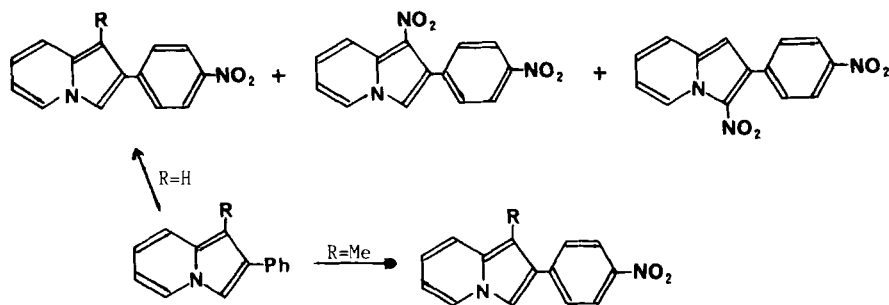


FIG. 3.

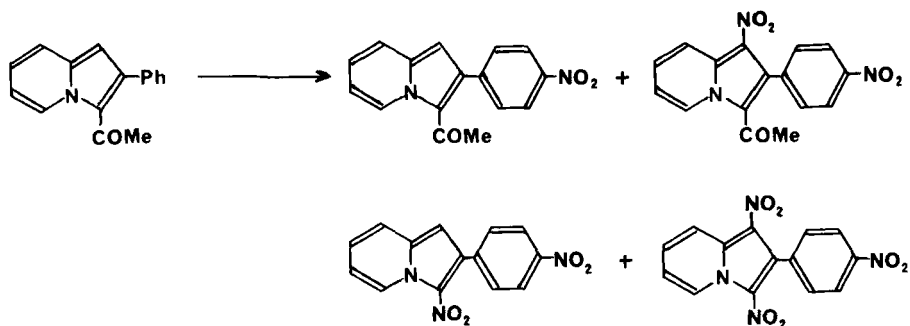
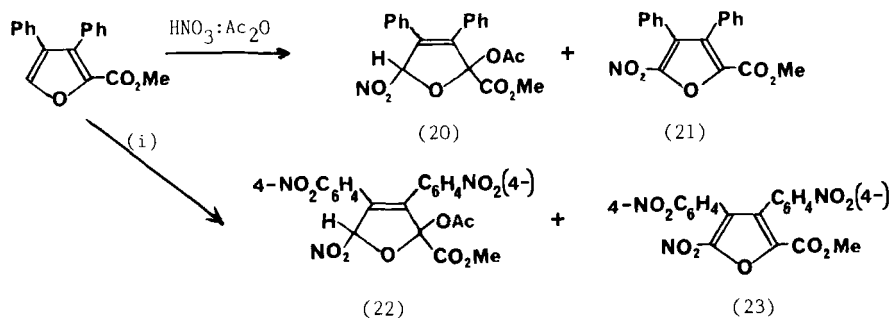


FIG. 4.

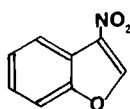
3. Furans

The nitration of phenylfurans takes place in the furan ring very readily. The nitration of methyl 3,4-diphenylfuran-2-carboxylate using nitric acid:acetic anhydride at low temperatures (-40 to 20°C) gives products due to nitration in the furan ring (**(20)** and **(21)**), up to 40% of **(20)** and 20% of **(21)** being obtained. With the addition of concentrated sulfuric acid to the nitrating mixture, compounds **(22)** and **(23)** (approx. 30 and 10%, respectively) are obtained and none of the products **(20)** and **(21)** (81CPB635).

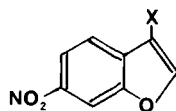
Benzofurans (coumarones), like furans, are normally nitrated in the 2-position but 2-phenylbenzofuran nitrates in acetic anhydride at 0°C to give a mixture of 3-nitro (**(24)**) and 6-nitro-2-phenylbenzofuran (**(25a)**) in yields of 50 and 15%, respectively. Additional nitration gives the same dinitro product (**(25b)**) [65AC(R)1028].



The nitration of other phenylbenzofurans follows the same pattern; for example, 2,3-diphenylbenzofuran gives the 6-nitroderivative (60MI1) and 5-hydroxy-2-phenyl and 5-hydroxy-3-phenylbenzofuran first undergo ni-



(24)

(25) (a) $X=H$
(b) $X=NO_2$

tration (and bromination) in the hydroxybenzo ring, then in the furan ring. However, reactions of the acetate derivatives of the 5-hydroxy group result in nitration in the furan ring (76CHE265). 5-Methyl-2,3-diphenyl, 2,3-diphenyl, and 4,7-dimethyl-2,3-diphenylcoumarone all nitrate to give 6-nitro derivatives (60MII;62MII;63MII).

4. Thiophenes

The nitration of 2-phenylthiophene using copper(II) nitrate in acetic anhydride gives 5-nitro-2-phenyl and 3-nitro-2-phenylthiophene in the ratio 3 : 2. The nitration of 3-phenylthiophene under the same conditions gives 2-nitro-3-phenyl and 5-nitro-3-phenylthiophene in the ratio 9 : 1. No 3-(4-nitrophenyl)thiophene is observed, although the main product of dinitration is 2-nitro-3-(4-nitrophenyl)thiophene. Dinitration of 2-phenylthiophene gives four products: 3,5-dinitro-2-phenyl, 5-nitro-2-(4-nitrophenyl), 3-nitro-2-(4-nitrophenyl), and 5-nitro-2-(4-nitrophenyl) thiophene (Fig. 5) [67ACS(B)2823]. Tetraphenylthiophene is nitrated by mixed acids at room temperature to form 2-(4-nitrophenyl)-3,4,5-triphenylthiophene (83%). Increasing the temperature and amount of nitrating mixture results in a mixture of further nitrated products [90JAP(K)01/125376].

The nitration of 4-hydroxy-2-phenylthiophene gives the 5-substituted products (79JIC404).

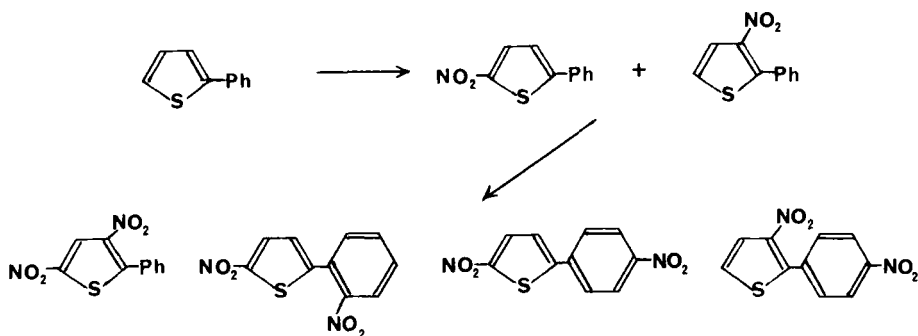


FIG. 5.

B. TWO HETEROATOM SYSTEMS

1. *Pyrazoles*

Phenylpyrazoles have been extensively studied. When nitrated in acetic anhydride 1-phenylpyrazole gives 4-nitro-1-phenylpyrazole (56G797; 63CJC1540), but in nitric acid and sulfuric acids, 1-(4-nitrophenyl) pyrazole results (56G797; 57JCS3024). Detailed mechanistic and kinetic studies of these reactions have been carried out by Schofield and co-workers [72JCS(P2)1654] and Katritzky and co-workers [74JCS(P2)389].

The results suggest that the free base of 1-phenylpyrazole undergoes nitration at the 4-position, whereas the conjugate acid undergoes nitration at the 4-position of the phenyl ring. 4-Nitro-1-phenylpyrazole undergoes nitration in sulfuric acid as the free base to give the 1-(4-nitrophenyl) derivative, and 1-(4-nitrophenyl)pyrazole is also nitrated as the free base to give the 4-nitro derivative. The 1-methyl-2-phenylpyrazolium cation has been shown to give the 2-(4-nitrophenyl)pyrazolium cation exclusively. The 1-methyl-4-nitro-2-phenylpyrazolium cation is nitrated similarly, and the 1-methyl-2-(4-nitrophenyl)pyrazolium cation is nitrated at the 4-position of the pyrazole ring [74JCS(P2)389]. These results are summarized in Fig. 6.

The results of Katritzky, Schofield, and their co-workers show a remarkable deactivation of the pyrazole and phenyl rings toward electrophilic substitution combined with a high selectivity for *para* substitution.

In nitric acid : sulfuric acid, 3-methyl-1-phenylpyrazole yields the 1-(4-nitrophenyl) derivative (96%), and 5-methyl-1-phenylpyrazole the 1-(4-nitro-phenyl) derivative (98%). 1-(2-Methylphenyl)- and 3,5-dimethyl-1-phenylpyrazole give low yields (up to 33%) of the 4-nitrophenyl products, but 1-(2,6-dimethylphenyl) pyrazole gives 1-(2,6-dimethyl-3-nitrophenyl) pyrazole (92%). The 1-methyl-2-phenyl and 5-methyl-1-phenylpyrazolium cations are markedly less reactive than the 1-phenylpyrazolium cation, presumably because of steric hindrance to coplanarity of the rings.

Nitration in acetic anhydride of 3-methyl-1-phenylpyrazole yields the 4-nitro product. 5-Methyl-1-phenylpyrazole gives a mixture of 5-methyl-3-nitro (75%) and 5-methyl-4-nitro-1-phenylpyrazole (25%). 3,5-Dimethyl-, 1-(2-methylphenyl)-, and 1-(2,6-dimethylphenyl)pyrazole each give the 4-nitro products in 42 and 65% and in unspecified yield, respectively [72JCS(P2)1654].

The two papers referred to above provide extensive information concerning relative rates of reaction and partial rate factors and are valuable guides to such studies of pyrazoles and other systems.

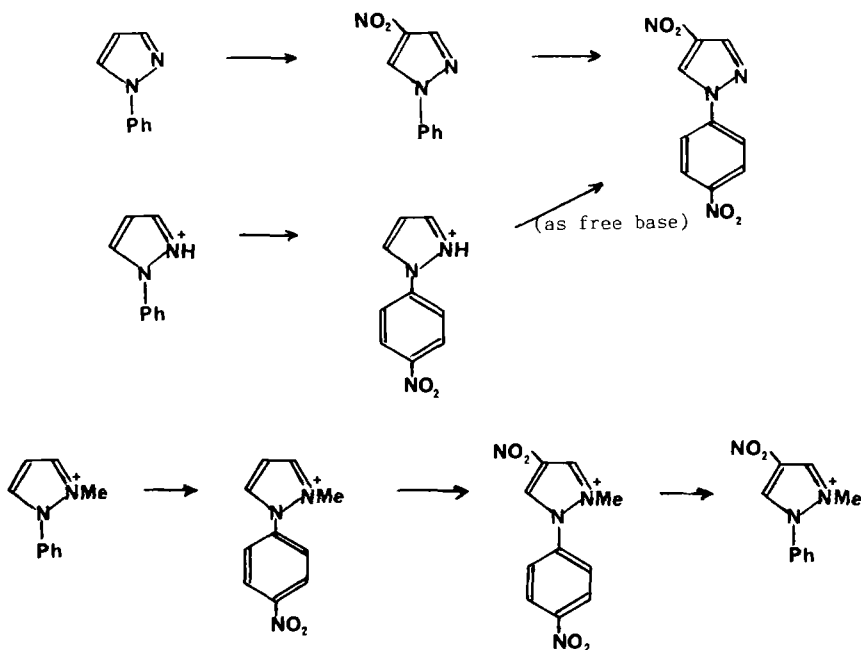


FIG. 6.

Details of the nitrations of some other x-nitrophenylpyrazoles carried out by Finar and Hurlock (57JCS3024) are given in Table II.

Khan, Lynch, and Hung (63CJC1540) also studied the nitration of 1-phenyl, 1-(4-biphenyl), and 1,5-diphenylpyrazole. In acetic anhydride, nitration occurs entirely in the 4-position of the pyrazole ring, as does bromination using bromine in chloroform. However, in sulfuric acid 1-(4-nitrophenyl) pyrazole is the initial product. Similarly bromination using bromine in sulfuric acid in the presence of silver sulfate gives 1-(4-bromophenyl) pyrazole. Brain and Finar also showed that 1-phenylpyrazole is first brominated in the pyrazole ring at the 4-position; the second bromination occurs in the 4-position of the phenyl ring. The position of the third bromination was not ascertained (58JCS2435).

The nitration of 3-phenylpyrazole (**26a**) using nitric acid:acetic anhydride gives a mixture of 3-(4-nitrophenyl)-1-acetylpyrazole (**26b**) and 1-nitro-3-phenylpyrazole (**26c**). Both then react with sulfuric acid to yield 3-(4-nitrophenyl)pyrazole (**26d**), which is the product of nitration using nitric acid:sulfuric acid. In this case, even in acetic anhydride, nitration did not occur in the pyrazole ring [58AC(R)783].

TABLE II
NITRATION OF SOME PYRAZOLES (57JCS3024)

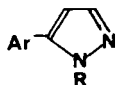
Nitration($\text{HNO}_3\text{:H}_2\text{SO}_4$)	Product	Yield(%)
	(100°C, 30 min)	
1-(2-Nitrophenyl)pyrazole	1-(2,4-Dinitrophenyl)pyrazole	73
1-(4-Nitrophenyl)pyrazole	1-(2,4-Dinitrophenyl)pyrazole	84
4-Nitro-1-(2-nitrophenyl)pyrazole	4-Nitro-1-(2,4-dinitrophenyl)pyrazole	80.5
4-Nitro-1-(4-nitrophenyl)pyrazole	4-Nitro-1-(2,4-dinitrophenyl)pyrazole	84
4-Nitro-1-phenylpyrazole	4-Nitro-1-(2,4-dinitrophenyl)pyrazole	85
1-(3-Nitrophenyl)pyrazole	1-(3,4-Dinitrophenyl)pyrazole	57
4-Nitro-1-(3-nitrophenyl)pyrazole	4-Nitro-1-(3,4-dinitrophenyl)pyrazole	72
	22°C, 16 h	
1-(2-Nitrophenyl)pyrazole	4-Nitro-1-(2-nitrophenyl)pyrazole	66
1-(3-Nitrophenyl)pyrazole	4-Nitro-1-(3-nitrophenyl)pyrazole	73
1-(2,4-Dinitrophenyl)pyrazole	1-(2,4-Dinitrophenyl)-4-nitropyrazole	64

In the nitration of methylphenylpyrazoles, Parrini [57AC(R)929] showed that a mixture of nitric and sulfuric acids leads to nitration first in the *para* position of the phenyl ring and second in the 4-position of the pyrazole ring. 4-Nitro-(4-nitrophenyl) derivatives were obtained from 3,5-dimethyl-1-phenylpyrazole and 3-methyl-5-phenylpyrazole.

Casoni (59G1539) has reported that 3-methyl-1-phenylpyrazole yields "mainly the 4-nitro derivative with some 1-(4-nitrophenyl) product," using nitric acid in acetic anhydride, whereas nitration in sulfuric acid gives 4-nitro-1-(4-nitrophenyl)pyrazole.

Huttel (55CB1577) also reported that the mixed acid nitration of 3-methyl-5-phenylpyrazole gives the 4-nitro-5-(4-nitrophenyl) product and that the nitration of 3,5-diphenylpyrazole with an excess of nitric acid forms 4-nitro-3,5-bis (4-nitrophenyl)pyrazole.

Hurst (88H371) confirmed that the nitration of 3-methyl-1-phenylpyrazole using nitric acid : sulfuric acid gives the 4-nitrophenyl product as the only isolable product of mononitration, and 3-methyl-4-nitro-1-(4-nitrophenyl)pyrazole as the dinitro product. However, 3-methyl-4-phenylpyrazole gives the 4-nitrophenyl product initially with the second nitration also occurring in the phenyl ring to give the 2,4-dinitrophenyl derivative. Another report on 3-methyl-4-phenylpyrazole gives the prod-



(26) (a) $\text{R}=\text{H}$, $\text{Ar}=\text{C}_6\text{H}_5$

(b) $\text{R}=\text{Ac}$, $\text{Ar}=4\text{-NO}_2\text{C}_6\text{H}_4$

(c) $\text{R}=\text{NO}_2$, $\text{Ar}=\text{C}_6\text{H}_5$

(d) $\text{R}=\text{H}$, $\text{Ar}=4\text{-NO}_2\text{C}_6\text{H}_4$

uct as the 4-nitrophenyl derivative but without any experimental details [48CI(L)69].

The nitration of 3-methyl-1,5-diphenylpyrazole (**27**), first studied by Knorr and Laubmann (1889CB174), was reinvestigated much later [07CB664; 55AC(R)728; 57AC(R)929; 69JCS(C)1328]. In nitric acid : sulfuric acid at 100°C a trinitro derivative, 3-methyl-4-nitro-1,5-bis(4-nitrophenyl) pyrazole, is obtained. Mixed acid nitration at 0°C gives 3-methyl-5-(4-nitrophenyl)-1-phenylpyrazole (60%), whereas excess nitric acid leads to 3-methyl-1,5-bis(4-nitrophenyl) pyrazole (73%).

The nitration of **27** using nitric acid in acetic anhydride at -5°C gives the 4-nitropyrazole (39%) without phenyl group substitution. This product can be nitrated further to 3-methyl-4-nitro-5-(3-nitrophenyl)-1-phenylpyrazole (7%) and 3-methyl-4-nitro-5-(3-nitrophenyl)-1-(4-nitrophenyl)pyrazole (50%) using nitric acid : sulfuric acid (Fig. 7).

Similar reactions were also carried out using the 4-bromodiphenylpyrazoles (Fig. 8).

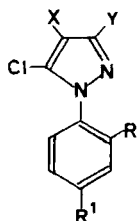
4-Ethyl-1-phenylpyrazole is nitrated in acetic anhydride producing the 3-nitropyrazole with no evidence for phenyl ring nitration (70TL479).

Dinitration of 1,3- or 1,5-diphenylpyrazole in sulfuric acid yields the corresponding bis (4-nitrophenyl) products, whereas nitric acid : acetic anhydride yields 4-nitro-1-(4-nitrophenyl) materials. Mononitration of the diphenylpyrazoles, and several other 1-arylpyrazoles, occurs at the 4-position in nitric acid : acetic anhydride at 0°C.

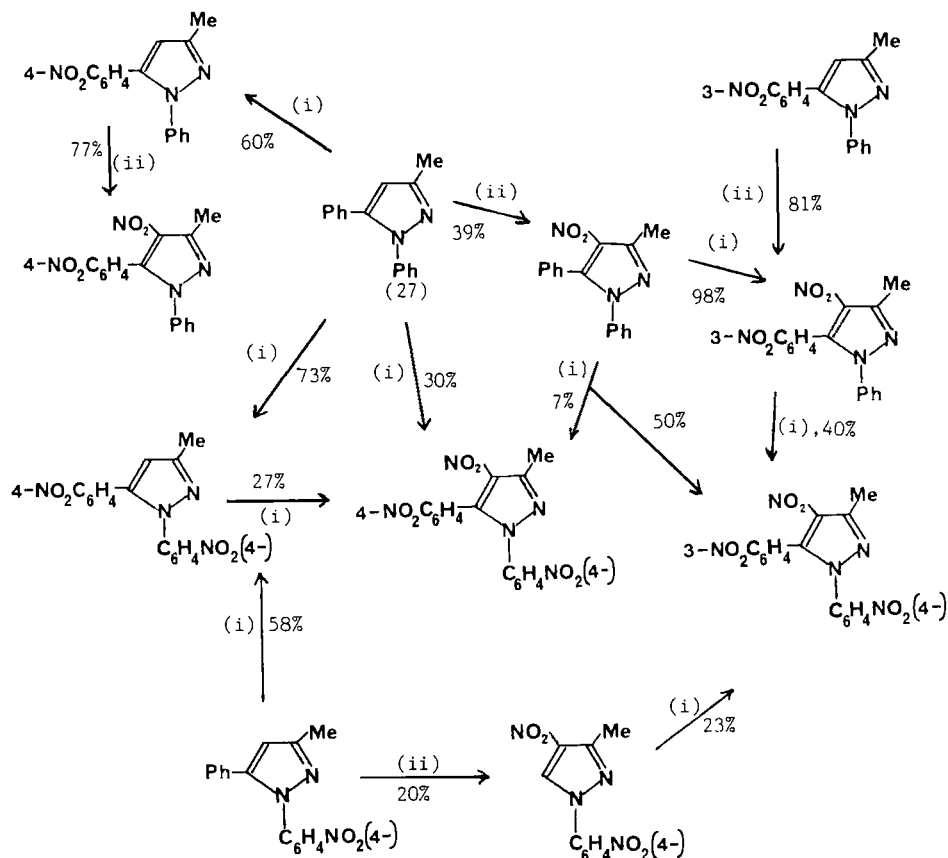
In strongly acidic media the conjugate acid is nitrated leading to *para* substitution in the phenyl ring. In acetic anhydride an intermediate such as (**28**) may be formed, resulting in the favored 4-attack in the pyrazole ring (Fig. 9).

The nitration of 3,4,5-triphenylpyrazole in fuming nitric acid (-5 to -10°C, then RT for 30min.) gives the tris (4-nitrophenyl) derivative (51%).

The nitration (fuming nitric acid) of 5-chloro-3-methyl-1-phenylpyrazole is reported to give a mononitro product (presumably the 4-nitrophenyl derivative) and a dinitro product 5-chloro-3-methyl-4-nitro-1-(4-nitrophenyl)-pyrazole (1900CB2595; 11LA329).



(29)



Conditions: (i) $\text{HNO}_3 : \text{H}_2\text{SO}_4$ (ii) $\text{HNO}_3 : \text{Ac}_2\text{O}$

FIG. 7.

A recent patent has reported the preparation of several 1-(3-nitrophenyl) pyrazoles, as intermediates leading to potential herbicides, by nitration of some 1-arylpyrazoles of the type (29). This indicates *meta* nitration of a 1-arylpyrazole in yields of 88% (87JAP62/123173).

A comprehensive report has described the nitration of 3-hydroxy-1-phenyl pyrazoles [75JCS(P2)1609]. These hydroxy compounds are tautomeric with pyrazolones but at equilibrium the hydroxy form is favored. 3-Hydroxy-5-methyl-1-phenylpyrazole is nitrated in acetone using pentyl

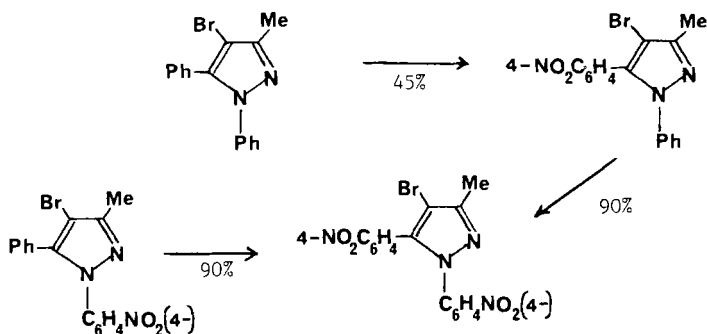


FIG. 8.

nitrite to give the 4-nitropyrazole (66%). Nitric acid at 0°C (then 20°C for 12 h) converts 3-methoxy-5-methyl-1-phenylpyrazole to the 4-nitropyrazole, and nitric acid alone also gives the 4-nitropyrazole from 2,5-dimethyl-1-phenylpyrazolin-3-one.

The nitration of 3-methoxy-5-methyl-1-phenylpyrazole with nitric acids: sulfuric acid at 0°C, followed by 3 h at 50°C, gives 3-methoxy-5-methyl-(4-nitrophenyl) pyrazole (51%), but reaction with mixed acid at 40°C for 24 h gives the 4-nitro-1-(4-nitrophenyl) product (85%). The preparative nitrations (using mixed acid) of the dinitro products are summarized in Table III. No n.m.r. evidence was found for the presence of ortho or meta nitrophenyl isomers.

Analysis of the kinetic results showed that all of the compounds studied underwent a change from nitration of the free base at low acidity to nitration of the conjugate acid at high acidity. The protonated pyrazolone ring, or 3-hydroxypyrazole ring, considerably deactivates the phenyl ring toward nitration but it still occurs at the *para* position. Comparison of the rates of nitration of the neutral pyrazolinones and their methyl derivatives indicates that the reaction of 3-hydroxy-5-methyl-1-(4-nitrophenyl)pyrazole is best explained by involving the *oxo* form rather than the prevalent hydroxy tautomer [75JCS(P2)1609].

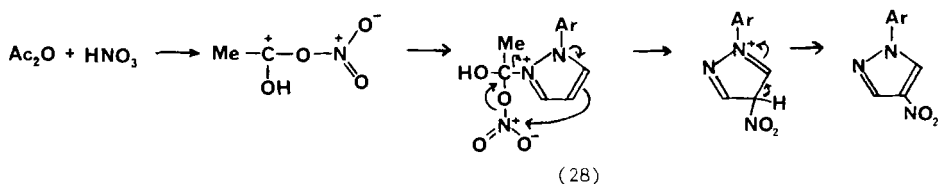
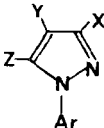
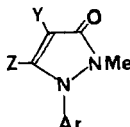


FIG. 9.

TABLE III
NITRATION PRODUCTS OF 3-HYDROXYPYRAZOLES [75JCS(P2)1609]

Reactant				Product	Yield (%)
<div style="text-align: center;">  </div>					
X = OH	Y = H	Z = Me	Ar = Ph		67
OH	NO ₂	Me	Ph	X = OH, Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	88
OH	H	Me	4-NO ₂ C ₆ H ₄	X = OH, Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	84
OMe	H	Me	Ph	X = OH, Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	85
OMe	NO ₂	Me	Ph	X = OMe, Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	91
OMe	H	Me	4-NO ₂ C ₆ H ₄	X = OMe, Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	92
<div style="text-align: center;">  </div>					
Y = H	Z = Me	Ar = Ph			57
NO ₂	Me	Ph		Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	84
H	Me	4-NO ₂ C ₆ H ₄		Y = NO ₂ , Z = Me, Ar = 4-NO ₂ C ₆ H ₄	86

The nitration of phenylpyrazolinones has also been studied by Katritzky and co-workers [74JCS(P2)382]. Electrophilic substitution in 2-pyrazolin-5-ones usually involves C4. Sulfonation, bromination, and chlorination of 1-phenylpyrazolin-5-ones all give 4-substitution (then 4,4-disubstitution in the cases of halogenation) before attack on the phenyl ring [1887LA137; 1892CB766; 1892CB1941; 41USP2234866; 47ZOB522; 52ACS(B)1499]. The nitration of 1-phenylpyrazolin-5-ones using nitric acid alone also gives the 4-nitropyrazolinone products (1887LA214;40G401), although nitration using nitric acid : sulfuric acid results in *para* substitution in the phenyl ring (up to 90%) [1892CB1853; 74JCS(P2)382]. Mixed acid nitration of 3-methyl-1-phenylpyrazolin-5-one is also reported to give the 4-nitrophenyl product (48JA1980).

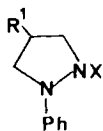
The results of Katritzky and co-workers [74JCS(P2)382], who carried out an extended study of such systems, are shown in Fig. 10. These indicate that all six compounds studied reacted as the conjugate acid at high acidity. Three compounds also reacted as the conjugate acid at low acidity [3-methyl-4-nitro-1-phenylpyrazolin-5-one, 3-methyl-5-methoxy-4-nitro-1-phenyl pyrazole, and 3-methyl-5-methoxy-1-(4-nitrophenyl) pyrazole]. The other three compounds [2,3-dimethyl-4-nitro-1-phenylpyrazolin-5-one, 3-methyl-1-(4-nitrophenyl) pyrazolin-5-one, and 2,3-dimethyl-1-(4-nitrophenyl) pyrazolin-5-one] reacted as free bases at low acidity.

The nitration of 1,2-diphenyl-3,5-dioxypyrazolidine with mixed acid at 0°C gives the 4-nitro derivative, whereas sulfonation (20% oleum) results in both 4- and phenyl substitution to form 4-sulfo-1,2-bis (4-sulfophenyl)-3,5-dioxypyrazolidine (58ZOB3027).

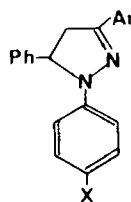
Reduced pyrazoles of type 30 react to give 4-nitrophenyl products on mononitration and then 2,4-dinitrophenyl products. Bromination and sulfonation also result in *para* substitution of the phenyl ring (78CHE1119).

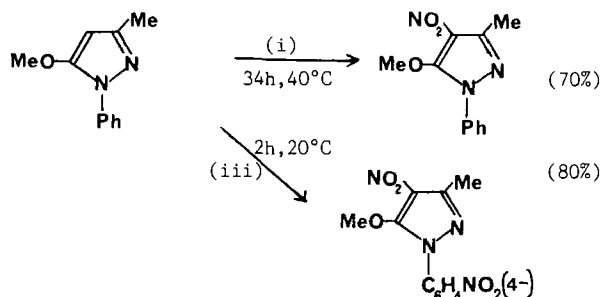
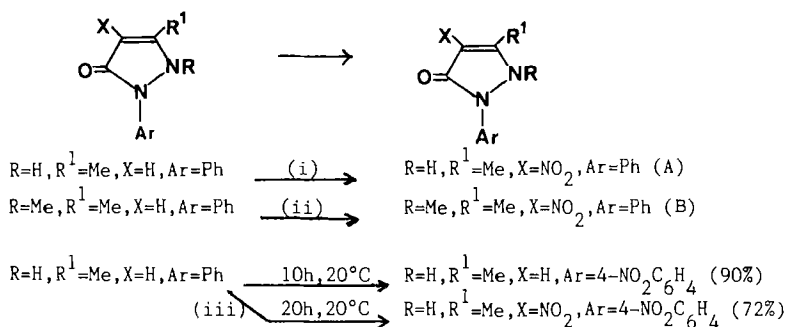
The nitration of 1,5-diphenyl-3-aryl-2-pyrazolines using potassium nitrate in sulfuric acid has been reported to give the product (31) in quantitative yield (84CHE787).

In the case of nitrosation, 1-phenyl-2-pyrazoline gives either attack at the 3-position or in the phenyl ring (05LA185), and diazo coupling has



(30)

(31) X=NO₂



Conditions: (i) amyl nitrile (ii) HNO_3 (iii) $HNO_3 : H_2SO_4$
 Nitrations of nitro compounds:

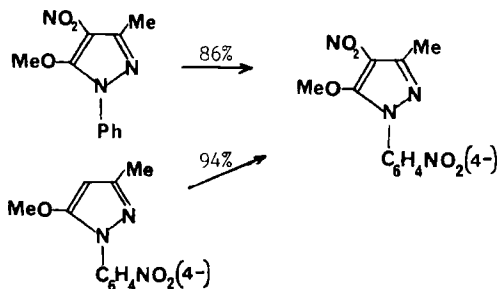
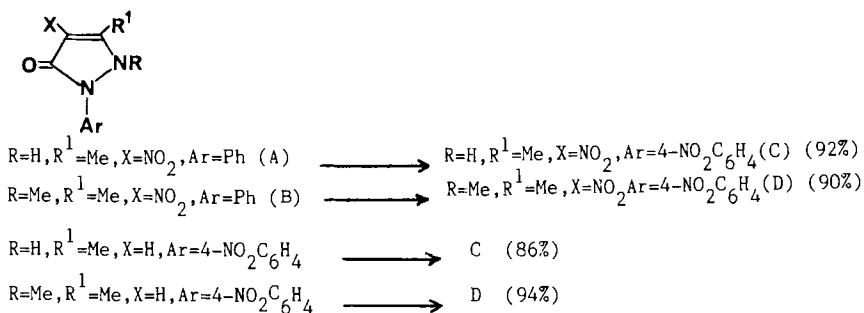


FIG. 10. Data from 74JCS(P2)382.

also been shown to result in 3-substitution (54JCS408), although earlier reports had suggested that 4-substitution occurred (05LA185; 08G619).

The results of the nitration of phenylpyrazoles have recently been summarized in a review of nitropyrazoles (88CHE353); the essential points are listed below:

Three types of compound are formed depending on the character of the substituents in the pyrazole ring and on the nitrating agent used:

(1) 1-(4-Nitrophenyl)-4-nitropyrazoles are usually formed when a mixed acid nitrating combination is used for 1-phenylpyrazoles containing substituents such as phenyl, methyl, chloro, and thienyl in the 3- and 5-positions of the pyrazole ring.

(2) 4-Nitropyrazoles are formed exclusively in the case of nitration using nitric acid in acetic anhydride and nitronium tetrafluoroborate in sulfolane.

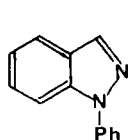
(3) 4-Nitrophenylpyrazoles are initially formed in the case of nitration using nitric acid or nitrating mixtures under mild conditions, and the reaction goes further with an increase in temperature or in nitric acid to give 4-nitro-1-(4-nitrophenyl)pyrazoles.

The results are in accord with the observations above; i.e., in mixed acid the pyrazole ring is protonated and the pyrazolium cation acts as a *para* director to the phenyl ring. In acetic anhydride pyrazoles are nitrated as free bases to yield 4-nitropyrazoles.

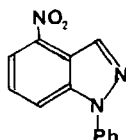
2. Indazoles

The nitration of indazoles seems to have been little studied. The nitration of 1-phenylindazole (**32**) in 86% nitric acid gives 4-nitro-1-phenylindazole (**33**) but an uncharacterized dinitro derivative is obtained with potassium nitrate in sulfuric acid (36LA285).

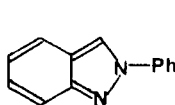
When 2-phenylindazole (**34**) is nitrated in the cold, two uncharacterized mononitro products are isolated, but the use of higher temperatures leads to oxidation to give azobenzenes (50BSF466; 52FRP1005327). The production of two unknown mononitro compounds (mp 170 and 184°C) was also reported very much earlier (1894CB47) when monosulfonation was also observed to give two unknown products and bromination to give a mono-



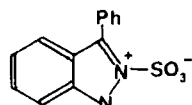
(32)



(33)



(34)



(35)

bromo derivative and a tribromo derivative. The sulfonation of indazole itself gives the 7-sulfonic acid (28JPR67; 50BSF466).

3-Phenylindazole, on nitrosation, gives a product (mp91–92°C) believed to be the 2-derivative, whereas chlorosulfonation of 3-phenylindazole is reported to give the salt (35) (22CB1112).

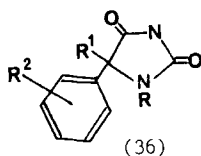
3. Imidazoles

The chemistry of the imidazoles was studied extensively in the 1920s by Pyman and co-workers, who included studies of nitration reactions.

These early nitrations were carried out by adding the imidazole nitrate salts to sulfuric acid at 100°C. Such a procedure results in phenyl ring substitution, the following results being recorded:

1-phenylimidazole:	1-(4-nitrophenyl)imidazole (58%) (30JCS397)
2-phenylimidazole:	2-(4-nitrophenyl)imidazole (50%) (24JCS2484); 2-(2-nitrophenyl)imidazole (1.5%); 2-(3-nitrophenyl)imidazole (0.2%)
4-phenylimidazole:	4-(4-nitrophenyl)imidazole (69%) (21JCS1893); 4-(2-nitrophenyl)imidazole (25%)
2-phenyl-2-imidazoline:	3-nitrophenyl-2-imidazoline (26JCS800)
2-phenylimidazole-4-carboxylic acid:	2-(4-nitrophenyl)imidazole-4-carboxylic acid (52%) 2-(3-nitrophenyl)imidazole-4-carboxylic acid (19%)
2-phenylimidazole-4,5-dicarboxylic acid:	2-(4-nitrophenyl)imidazole-4,5-dicarboxylic acid (19%); 2-(3-nitrophenyl)imidazole-4,5-dicarboxylic acid (52%)

The imidazolone (**36**, R = H; R¹ = Ph; R² = H) is reported to give a mixture of products (**36**, R¹ = 3-NO₂C₆H₄, 2-NO₂C₆H₄; R² = 4-NO₂C₆H₄), whereas the nitration of (**36**, R = Me; R¹ = Et; R² = H) yields (**36**, R² = 4-NO₂C₆H₄) together with (**36**, R² = 3-NO₂C₆H₄) could also be shown (75MI1).



Pyman and co-workers also reported the nitration of 4-bromo- and 4,5-dibromo-2-phenylimidazole (KNO₃ in sulfuric acid at 100°C, 2 h) to give 4-

bromo-2-(4-nitrophenyl) (63% with 1.8% of an unknown isomer) and 4,5-dibromo-2-(4-nitrophenyl) imidazole (31% with other material of unknown structure).

The reaction of 1-phenylimidazole with nitronium tetrafluoroborate (25°C, 30 min) produces 5-nitro-1-phenylimidazole (67NEP6609553), whereas a patent claim that mononitration of 2-phenylimidazole gives 4-nitro-2-phenylimidazole, and not the 4-nitrophenyl derivative, was an error (70GEP1953999).

The nitration of 4- and 5-phenyl-1-methylimidazole using mixed acid gives only the 4-nitrophenyl products (56 and 64%, respectively) with "some 2-nitrophenyl product" (24JCS1431).

Further nitration of 4-methyl-2-(4-nitrophenyl) imidazole using mixed acid gives the 5-nitro product (21JCS1893), and dinitration of 4-methyl-2-phenylimidazole using fuming nitric acid, produces 5-nitro-2-(4-nitrophenyl)-imidazole (40JPJ312).

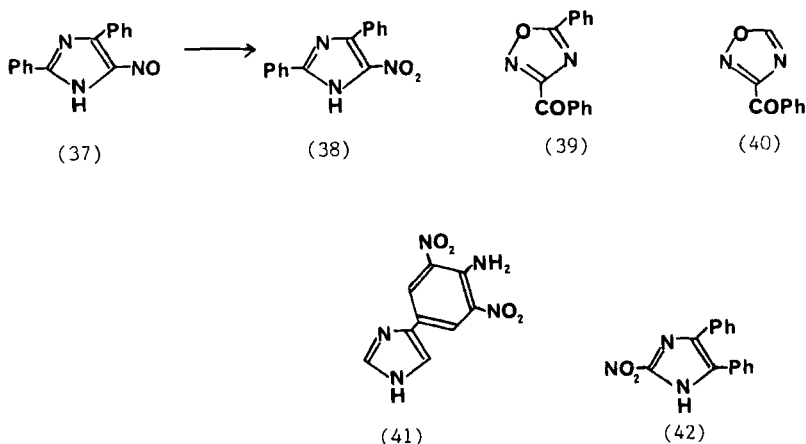
The nitrate salts of nitrophenylimidazoles undergo further reaction when heated with concentrated sulfuric acid to form the 4-nitrophenyl products. For example, 4-(4-nitrophenyl) imidazole nitrate yields 4-(4-nitrophenyl)-5-nitroimidazole (2JCS1893) and 4-(4-nitrophenyl)-1-methylimidazole gives 4-(4-nitrophenyl)-5-nitro-1-methylimidazole (24JCS1431). A German patent also reports that the second nitration of 1-(4-nitrophenyl)imidazole occurs at the 4-position of the imidazole ring (73GEP2208924).

4-Nitro-1-phenyl- and 2-methyl-4-nitro-1-phenyl-imidazole react with 65% nitric acid in sulfuric acid (1 h at 120°C) to yield the 4-nitrophenyl products (73GEP2145651). A series of 5-nitro-4-nitroarylimidazoles has been prepared (67MI1), and some other nitrations of this type have also been reported (71BSF1303; 75USP3380871). A Belgian patent records the preparation of a variety of 2-aryl-4-nitroimidazoles by the action of nitric acid in acetic anhydride (65BEP6608361). Further examples of the nitration of arylimidazoles are given below.

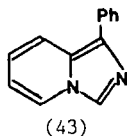
The addition of amyl nitrate to a suspension of 2,4-diphenyl-5-nitrosoimidazole (**37**) in ether results in a mixture of 2,4-diphenyl-5-nitroimidazole (**38**) and 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**39**), but a similar reaction using 4-phenyl-5-nitrosoimidazole gives only 3-benzoyl-1,2,4-oxadiazole (**40**) (60MI1).

Heating 4-(4-acetamidophenyl) imidazole with 3 *M* nitric acid at 85°C forms the dinitrate salt of the corresponding amine, but the use of 5 *M* acid gives 4-(4-amino-3,5-dinitrophenyl) imidazole (**41**) (79AKZ475).

4,5-Diphenylimidazole is nitrated by nitric and sulfuric acids in the presence of urea to give 96% of 4,5-bis(4-nitrophenyl)imidazole [90GEP(O)3835195], whereas amyl nitrite reacts with 4,5-diphenylimidazole to give 2-nitro-4,5-diphenylimidazole (**42**). This reaction may be re-



lated to incompletely understood reactions between benzene compounds and "lower level" nitrogen oxide derivatives to form nitric oxide and a nitrophenyl compound without the intermediacy of a nitroso phenyl compound (49MI1; 81CHE1284; 83JOC1495).



4. Benzimidazoles

In the case of benzimidazole itself, nitration usually occurs at the 5-position (80MI1). Sterba and co-workers have studied the nitration of some arylbenzimidazoles and have showed that 2-phenyl benzimidazole, when treated with nitric acid : sulfuric acid at 10°C, gives 6-nitro-2-phenylbenzimidazole (75%). The 2-(3-nitrophenyl) and 2-(4-nitro phenyl) benzimidazoles similarly yield the 6-nitro products (57 and 97% respectively), and nitration of 6-nitro-2-phenylbenzimidazole gives the 2-(4-nitrophenyl) and 2-(3-nitrophenyl) products in 44% and 32.5% yields, respectively (65CCCC1093).

The nitration of 1-phenylimidazo[1,5-a]pyridine (43) as the free base using nitric acid in acetic acid gives either the 3-mononitro or the 3-nitro-1-(4-nitrophenyl) dinitro product. 3-Methyl-1-phenylimidazo[1,5-a]pyridine (as the hydrogen sulfate salt) gives the 4-nitrophenyl mononitro product, and a similar reaction of 3-phenylimidazo[1,5-a]pyridine gives the 1-nitro product [80JCS(P1)959].

5. Oxazoles and Isoxazoles

There have been a number of reports of the nitration of phenyloxazoles which, in general, undergo ready substitution in the phenyl ring. 2-Phenyloxazole is nitrated (and brominated) in acetic anhydride at the 5-position of the heterocyclic ring (85CS295). However, in sulfuric acid, in which the oxazole ring is protonated, nitration occurs primarily in the *meta* position of the phenyl ring. A previous report (84CHE713) had shown that the nitration of 2-phenyloxazole using nitronium tetrafluoroborate in acetonitrile at 0 to 5°C gives about 35% of a mixture containing 5-nitro-2-phenyl, 2-(4-nitro-phenyl), and 2-(3-nitrophenyl) oxazole (Fig. 11). These workers also brominated 2-phenyloxazole (using bromine in refluxing benzene) to obtain 5-bromo-2-phenyloxazole (56%) and 4,5-dibromo-2-phenyloxazole (9%). The nitration of 2-aryl-4-phenyloxazoles (aryl = Ph, 2-NO₂C₆H₄, 3-NO₂C₆H₄, 4-NO₂C₆H₄), however, yields 2-aryl-4-(4-nitrophenyl) oxazoles (74M11).

The nitration of 3-phenylisoxazole has been carried out by several workers, but the products of the reaction have not been conclusively identified. An early report (03LA263) states that the product of mixed acid nitration is 3-phenyl-4-nitroisoxazole having a mp of 116°C. However, a later worker (51FES32) reported that nitration gives a product (unidentified) having a mp of 174–176°C.

When 4-phenylisoxazole is nitrated in sulfuric acid at –10°C using nitric acid (*d* 1.5), a 98% yield of 4-(4-nitrophenyl) isoxazole is obtained. A mixture of 4-phenylisoxazole in sulfuric acid and 99% nitric acid at 70°C (30 min) gives the dinitro product 4-(2,4-dinitrophenyl)isoxazole (67G1604).

The nitration of 5-phenylisoxazole has been investigated by several groups. Nitric acid:sulfuric acid at 20°C has been reported to give two products, 4-nitro-5-phenyl and 5-phenyl-4-(4-nitrophenyl)isoxazole (58ZOB359). In another study it was shown that the use of either nitric acid (*d* 1.42 or 1.5) in sulfuric acid, or in acetic anhydride, gives principally 5-(4-nitrophenyl)isoxazole (65CJC2117). Reinvestigation of this reaction gave the following results (68ZOR2057). The main reaction product (about 50%) is the 5-(4-nitrophenyl) product with some 4-nitro-5-(4-nitrophenyl)-isoxazole. About 6% of 5-(3-nitrophenyl)isoxazole product is also inferred

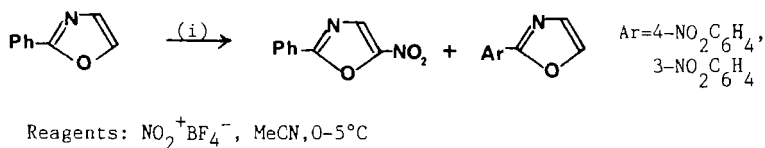


FIG. 11. Reagents: NO₂⁺BF₄[–], MeCN, 0–5°C.

from oxidation results that show the formation of 3-nitrobenzoic acid. A similar spectrum of products has been obtained on the sulfonation of 5-phenylisoxazole.

3-Methyl-5-phenylisoxazole is reported to react in mixed acid to produce only the 4-nitrophenyl product, whereas 5-methyl-3-phenylisoxazole gives the 3-nitrophenyl and 4-nitrophenyl products (42G537;57JA467).

Later work has shown that 3-methyl-5-phenylisoxazole is nitrated as the conjugate acid in mixed acid to give the 4-nitrophenyl product exclusively, whereas in nitric acid : acetic anhydride, poor yields of 4-nitro-5-(4-nitrophenyl)isoxazole are obtained as the only product.

5-Methyl-3-phenylisoxazole is also nitrated via the conjugate acid in mixed acid to yield the 3-nitrophenyl product and as the free base to give the 4-nitrophenyl product. The proportion of *meta* : *para* nitration varies with the acidity of the medium. 5-Methyl-3-phenylisoxazole, in nitric acid : acetic anhydride, yields 4-nitro-3-(4-nitrophenyl)isoxazole. The standard rates of nitration at 25°C and H_0 -6.6 have been calculated [75JCS(P2)1627].

In another study of the nitration of 5-phenyl- and 3-methyl-5-phenylisoxazole the action of nitric acid : sulfuric acid on 5-phenylisoxazole produced a 1 : 1 : 1 mixture of the *ortho*, *meta*, and *para* 5-(nitrophenyl) products with minor amounts of 4-nitro-5-(3-nitrophenyl)- and 4-nitro-5-(4-nitrophenyl)-dinitro products. The action of nitric acid : acetic anhydride produced 4-nitro-5-phenylisoxazole as the major product with some nitrophenyl compounds as minor products. 3-Methyl-5-phenylisoxazole also gave a mixture of the *ortho*, *meta*, and *para* 5-(nitrophenyl) products when mixed acids were used, but no dinitro products were observed. The use of nitric acid : acetic anhydride resulted in nitration at the 4-position of the isoxazole ring as the largely predominant product, with some phenyl ring substitution (89H1965).

However, the only product obtained on nitration of 5-methyl-3-phenylisoxazole-4-carboxylic acid is the 3-nitrophenyl product (91UP1).

3,5-Diphenylisoxazole is nitrated using nitric acid in acetic anhydride (20°C, 8 days) to give 4-nitro-3,5-diphenylisoxazole. The use of an equimolar amount of nitric acid alone at 0°C (1 h) gives 5-(4-nitrophenyl)-3-phenylisoxazole, and nitration using a 5 mole-equivalent amount of nitric acid (0°C, 2 h) produces 3-(3-nitrophenyl)-5-(4-nitrophenyl)isoxazole. The structures of the products have been confirmed by unequivocal synthesis. These results indicate an interesting difference in the directing ability of the protonated 3-isoxazolyl and 5-isoxazolyl groups toward substitution in the phenyl ring (74CHE516).

Sokolov and co-workers also nitrated several other arylisoxazoles (mixed acid at 20°C) to give the products in Table IV (71ZOR1979). If the

TABLE IV
NITRATION PRODUCTS OF SOME ARYLISOXAZOLES (71ZOR1979)

Arylisoxazole	Product
5-(4-Chlorophenyl)isoxazole	5-(4-Chloro-3-nitrophenyl)isoxazole
5-(4-Nitrophenyl)isoxazole	4-Nitro-5-(4-nitrophenyl)isoxazole
3-(4-Nitrophenyl)isoxazole	4-Nitro-3-(4-nitrophenyl)isoxazole with some 3-(2,4-dinitrophenyl)isoxazole
3-(4-Chlorophenyl)isoxazole	3-(4-Chloro-3-nitrophenyl)isoxazole
	3-(4-Chloro-2-nitrophenyl)isoxazole
	4-Nitro-3-(4-chlorophenyl)isoxazole

substituent in an aryl ring is sufficiently deactivating, then the nitration of aryl isoxazoles occurs in the heterocyclic ring (71JOU2051).

The nitration of 3-phenyl-2-isoxazoline with 1 mole-equivalent of nitric acid (*d* 1.5) in sulfuric acid at 0°C results in 96% of nitrophenyl products of which only the 4-nitrophenyl isomer has been isolated, although oxidation of the products has given about 5% of 3-nitrobenzoic acid (67ZOR1532). The nitration of DL-*trans*-2-methyl-5-phenyl- Δ^2 -oxazoline sulfate (nitric acid, *d* 1.52, -5°C) also gives the 5-(4-nitrophenyl) product (84%)(56MII).

6. *Thiazoles and Isothiazoles*

2-Phenylthiazole, like 2-phenyloxazole, is also nitrated (and brominated) at the 5-position of the heterocyclic ring. The thiazole is less reactive than the oxazole ring. In nitration of the protonated thiazole, the predominant product is 2-(4-nitrophenyl)-thiazole (85CS295), in contrast to the nitration of 2-phenyloxazole, which gives predominantly 2-(3-nitrophenyl)oxazole (84CHE713).

Phenylthiazoles were also nitrated by earlier workers (47HCA2058; 51JPJ869), who showed that the use of nitric acid in sulfuric acid at 0°C produced the 4-nitrophenyl product in each case from 2-, 4-, and 5-phenylthiazole (yields of 80, 90, and 92%, respectively). Yet another study of the nitration of phenylthiazoles has given the results shown in Table V (71BSF4310).

In some cases arylthiazoles undergo preferential substitution in the 5-position of the thiazole ring. In the case of 2-phenyl-2-thiazoline, only the 3-nitrophenyl product is obtained (37JA2262; 39JPJ462; 40JPJ271).

4-Methyl-2-phenylthiazole forms the 4-nitrophenyl product on nitration, with some 2,4-dinitrophenyl product also being isolated (45JCS182).

TABLE V
NITRATION OF PHENYLTHIAZOLES (71BSF4310)

Thiazole	Isomer ratio(%)		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
2-Phenyl	3	8	89
4-Phenyl	7	4	89
5-Phenyl	15	2	83(+ 5% dinitro)

Reaction of 2-amino-4-phenylthiazole with one equivalent of nitric acid in sulfuric acid at 3 to 5°C results in a mixture of products containing 2-amino-4-(4-nitrophenyl), 2-amino-5-nitro-4-(4-nitro-phenyl), and a small amount of 2-amino-5-nitro-4-phenylthiazole. Work-up of the reaction mixture after only 10 min gives the same products but in different proportions. The use of two equivalents of nitric acid produces about 90% of 2-amino-5-nitro-4-(4-nitrophenyl)thiazole (59JOC187).

Studies of the nitration of 4-chloromethyl-2-phenylthiazole have shown that the action of nitric acid (d 1.40) in sulfuric acid at 60°C gives the 4-nitrophenyl product and the use of nitric acid in acetic anhydride at 60°C forms the 5-nitrothiazole product. Chlorination and bromination also result in 5-substitution in the thiazole ring and nitration of these products using mixed acid gives the 4-nitrophenyl products. 2-(4-Bromophenyl)-4-chloromethylthiazole also nitrates at the 5-position of the thiazole ring using nitric acid in acetic anhydride below 60°C (65CB3446).

2-Chloro-4-phenylthiazole (and some other 4-arylthiazoles) has also been shown to yield the 5-nitro derivative when reacted with nitric acid in acetic acid, bromination similarly giving the 5-bromo derivative (68JIC409).

In the case of 3-phenylisothiazoles, the parent compound is nitrated to give a mixture of 3-(4-nitrophenyl) and 3-(3-nitrophenyl)isothiazole, but a series of substituted compounds gave exclusively the 3-nitrophenyl products in each case (68CPB160).

A study of the nitration of 2-benzyl and 2-phenylethylthiazoles has also been made and has given the results shown in Table VI (71BSF4310).

In the case of 2-phenylbenzothiazoles electrophilic substitution occurs exclusively in the fused benzo ring, normally at the 6-position (84MI1).

TABLE VI
NITRATION OF SOME ARYLALKYLTHIAZOLES (71BSF4310)

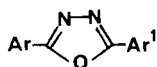
Thiazole	Isomer ratio(%)		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
2-Benzyl	11	25	64
4-Methyl-2-benzyl	13	27	60
5-Methyl-2-benzyl	18	35	47
4,5-Dimethyl-2-benzyl	18	37	45
2-Phenylethyl	30	5	65
4-Methyl-2-phenylethyl	23	9	68
5-Methyl-2-phenylethyl	25	8	67
4,5,-Dimethyl-2-phenylethyl	27	8	65

C. OTHER FIVE-MEMBERED RING SYSTEMS

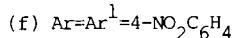
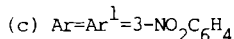
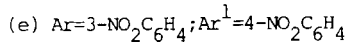
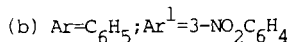
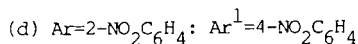
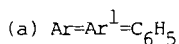
1. Rings with Three and Four Heteroatoms

3,5-Diphenyl-1,2,4,-triazole, in mixed acid at 40–50°C, gives 3,5-bis(4-nitrophenyl) and 3-(4-nitrophenyl)-5-(3-nitrophenyl) products in the ratio 65 to 35, respectively (75M11, 75M12). The same products are obtained using fuming nitric acid (*d* 1.5) at 0°C but the ratios differ, in this case being 57 to 47, respectively.

The nitration of 2,5-diphenyl-1,3,4,-oxadiazole (**44a**) was first investigated by Grekov and Azen (61JGU1796), who reported that fuming nitric acid (*d* 1.51) alone results in a mixture of three isomers, the 2,5-bis(2-nitrophenyl), bis(3-nitrophenyl), and bis(4-nitrophenyl) products in yields of 40, 20, and 27%, respectively. They found that fuming nitric acid in sulfuric acid gives a preponderance of 3-nitrophenyl products with both the mononitro and the dinitro derivatives being obtained in yields of 31 and 38%, respectively.



(44)



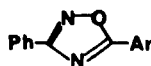
This reaction has been further investigated [80JCS(P2)773] and the products have been confirmed as being, with nitric acid alone, **44d,e**, and **f**, whereas mixed acid (and nitronium tetrafluoroborate) gives mainly 3-nitrophenyl products, viz. **44b,c**, and **e**. The nitration of the mononitrophenyl-1,3,4-oxadiazoles shows considerable variation of product ratios according to the conditions used.

The nitration of 3-phenyl-1,2,4-oxadiazoles (**45a-c**) with mixed acid at -5 to 0°C gives a different orientation according to the substituent R. For the series **45a**, *meta* products are obtained, for **45b** both *meta* and *para* products are obtained, whereas for **45c** only the 4-nitrophenyl product is obtained (63G1205).

Munno and co-workers have studied the nitration of 3-phenylfuran and the sulfur and selenium analogues. They have shown that electrophilic substitution does not involve the heterocyclic ring, which is *ortho/para* directing. Mononitration occurs in both positions, with *para* predominating, with some 2,4-dinitration also occurring with the sulfur and selenium analogues. The most reactive compound is the sulfur analogue. Bromination is also reported to occur at the 4-position of the phenyl ring for these compounds (78M11).

Nitration of 3-phenylfuroxan (**46**) with 90% nitric acid at -5°C gives an 18:82 mixture of *ortho* and 4-nitrophenyl products (92%), considered to be formed via stabilized Wheland intermediates. If 99% nitric acid (at 4°C) is used, the 2,4-dinitrophenylfuroxan (88%) is obtained (83G811).

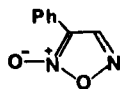
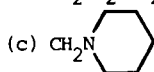
The nitration of 5-phenyl-1,3,4-oxathiazolin-2-one (**47**) has been reported to give a 50% isolated yield of the 4-nitrophenyl derivative. The residue was analyzed after pyrolysis and found to contain 62% *ortho* and 38% *meta* and *para* nitro products. The nitration was thus indicated to give >54% *para*, <18% *meta*, and 28% *ortho* products (69TL5131; 73ACS2161). The heterocyclic ring was deactivating and *ortho/para* directing.



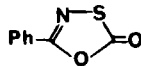
(45)

(a) R=Me; Et; Bu; ClCH_2 ; $(\text{CH}_2)_2\text{NEt}$; $(\text{CH}_2)_3\text{NEt}_2$; Ph; CH_2NHAc

(b) CH_2NH_2 ; CH_2NEt_2

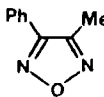
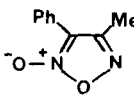
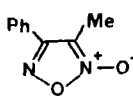


(46)



(47)

TABLE VII
ISOMER RATIO (%) UPON MONONITRATION OF
1, 1a, 1b [83JHC1419]

			
(1)	(1a)	(1b)	
Compound	<i>ortho</i>	<i>meta</i>	<i>para</i>
1	30	13	57
1a	29	3	68
1b	29	16	55

The 3-phenyl-4-(substituted)furazans (**48**) have been prepared and nitrated using mixed acid. The furazanyl group was declared to be "mildly *ortho/para* directing" in relation to the phenyl group. This effect is diminished by the introduction of an electron-withdrawing group at the 4-position of the furazan ring. At 50 to 90°C 2,4-dinitrophenyl derivatives are obtained (82CHE21).

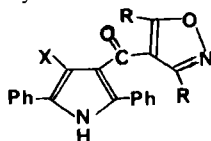


(48) R=H, Me, Ph, NO₂, CO₂H

In a subsequent study the isomer ratios of the products obtained on mononitration of methylphenylfurazans and furoxans in 90% nitric acid were those shown in Table VII (83JHC1419).

The first study of the nitration of 2-phenyl-1,2,3[2*H*]-triazole suggested that the products, using mixed acid at 20°C, were the *ortho* and *para* isomers (48JOC815). However, later work showed the two products to be the *para* isomer and the 4-nitro-2-(4-nitrophenyl) dinitrated product. Further nitration gives the 4-nitro-2-(2,4-dinitrophenyl) trinitrated product. Exclusive mononitration to produce the 4-nitrophenyl product can be effected using nitric acid in acetic anhydride (63CJC274).

Compounds (**49**) undergo nitration in the heterocyclic ring on reaction with nitric acid : acetic anhydride in nitromethane at -15°C (77JHC1021).



(49) R=Me, Ph; X=H, NO₂

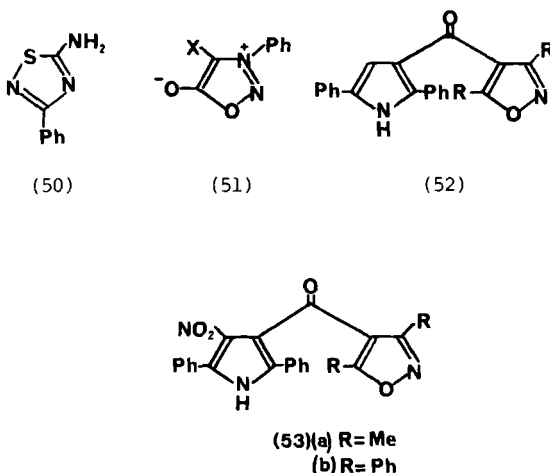
The nitration of 1-phenyl-1,2,4-triazole and 4-phenyl-1,2,4-triazole using mixed acid, as well as the nitration of 3-phenyl-1,2,4-triazole, each gives the 4-nitrophenyl product with no mention of other isomers (69ZC378). 3-Methyl-1-phenyl, 5-methyl-1-phenyl, and 3-methyl-4-phenyl-1,2,4-triazole have also been reported to yield 4-nitrophenyl products (67BSF2634).

Both 5-methylthio-1-phenyltetrazole and the phenylthiadiazolamine (**50**) nitrate at 0°C to produce the 1-(4-nitrophenyl) compound (93%) (56JOC1191; 91UPI).

The sydnone ring system is subject to electrophilic attack but also acts as an activating *ortho/para* group. Thus 3-phenylsydnone (**51**, X = H), in concentrated sulfuric acid at -7°C with potassium nitrate, or with concentrated nitric acid at -5°C, gives 4-nitro-3-phenylsydnone (**51**, X = NO₂) (50JCS1542; 57NKZ181, 57QR15).

3-Methyl-4-phenylsydnone is nitrated using nitric acid:acetic acid at RT to give the 4-nitrophenyl product (80%), with small amounts (<3%) of *ortho* and possibly the *meta* product. The use of mixed acid, or fuming nitric acid, at 0°C forms the 2,4-dinitrophenyl product (60–70%) [62CI(L)1718].

In the nitration of 2,5-diphenyl-3-pyrrol-3¹,5¹-dimethyl (or diphenyl)-4-isoxazolyketone (**52**), the only reaction that is detected is the formation of the 4-nitro derivatives (**53a,b**) (77JHC1021).



2. Fused Five-Membered Ring Systems

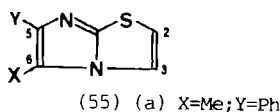
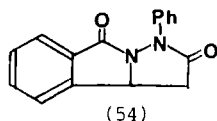
There is little information available on the nitration, or other electrophilic substitutions, on fused five-membered ring systems.

The nitration of the reduced 1*H*-pyrazolo[5,1-*a*]isoindole (**54**) gives the 2,4-dinitrophenyl derivative, without attack at the benzo ring (47JCS829; 48JCS1249).

Generally imidazo[2,1-*b*]thiazoles (**55**) having 6-substituents undergo electrophilic substitution at the 5-position, and those with 5-substituents undergo electrophilic substitution at the 6-position. 6-Phenylimidazo[2,1-*b*]thiazole is nitrated, using mixed acid, to give the 6-(4-nitrophenyl) derivative, and the 5-nitro-6-(4-nitrophenyl) dinitrated product. Further substitution occurs at the 2-position. Nitrosation and diazo-coupling reactions also give the 5-substituted product (61LA153; 62LA108; 67G488).

Very little is known about the reactivity of imidazo[5,1-*b*]thiazoles. It seems that for 3,5-di, and 2,3,5-trisubstituted compounds, nitrosation occurs at the 7-position (64LA144).

5-Methyl-6-phenylimidazo[2,1-*b*]thiazole (**55a**) has been reported to give the 4-nitrosophenyl product, but 2,5-dimethyl-6-phenylimidazo[2,1-*b*]thiazole is reported not to react with nitrous acid, so the product of the reaction is most likely to be the 3-substituted compound (61LA145).



2,3-Dihydroimidazo[2,1-*b*]thiazole reacts with concentrated nitric acid at 70–80°C to form what is believed to be the 5-nitro derivative [77IJC(B)629], whereas the 6-phenyl derivative of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (as nitrate salt) gives the 4-nitrophenyl product (60%) (66JMC545).

The reaction of 3-phenyl[5,1-*b*]benzothiazole with a variety of electrophiles results only in 1-substitution (66KGS292).

2-Phenylimidazo[2,1-*b*]benzothiazole (**57**), on nitration, gives the 4-nitrophenyl derivative, and a dinitro derivative assumed to be 2-(4-nitrophenyl)-3-nitroimidazo[2,1-*b*]benzothiazole (66M11). Other electrophiles have been assumed to give 3-substituted products (67G1286).

In the case of 1,3-diphenylfuro[3,2-*c*]pyrazole (**58**) most electrophilic substitutions, e.g., Vilsmeier formylation, Friedel–Crafts acylation, and monobromination, take place in the furan ring. Excess bromine gives the second bromination in the 4-position of the 1-phenyl group, but nitration gives the 1-(4-nitrophenyl) derivative and a second, uncharacterized, product (78YZ204).

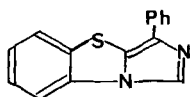
In the case of 5-bromo-3,4-dimethyl-1-phenyl-1*H*, 6*H*-pyrano[2,3-*c*]pyrazol-6-one (**59**), mixed acid nitration results not only in *para* substitution in the phenyl ring, but also in ipso attack at the 5-position to yield

the 5-nitro-1-(4-nitrophenyl) dinitro product, no mononitro product being isolated (87RRC295).

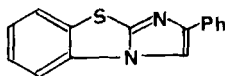
1,2-Diphenylimidazo[1,2-*a*]benzimidazole (**60**) undergoes electrophilic substitution at the 3-position. Nitration (potassium nitrate: sulfuric acid) also gives 3-nitration, followed by a second nitration in the 4-position of the 1-phenyl ring (81CHE937). Bromination follows a similar pattern.

The 5-phenyl derivative of thiazolo[3,2-*d*]tetrazole (**61**) has been reported to sulfonate and to chlorosulfonate at the 6-position, but nitration of these two compounds has not been reported (73M11).

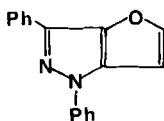
6-Phenylimidazo[2,1-*b*][1,3,4]thiadiazole (**62**) nitrates at the 5-position and also at the 4-position of the phenyl ring (75G777).



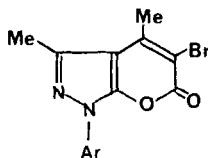
(56)



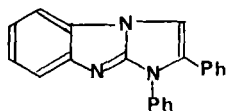
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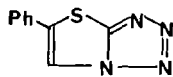
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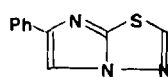
(59)



(60)



(61)



(62)

The imidazo[1,2-*d*][1,2,4]thiadiazole system seems to be unreactive, in general, to electrophilic substitution, but nitration (and bromination) is reported to give 5-substituted products (77G1).

III. Six-Membered Ring Systems

A. PYRIDINES AND FUSED PYRIDINES

1. *Pyridines and Quinolines*

The nitration of phenyl and benzylpyridines has been of interest for many years. Early work was carried out by Forsyth and Pyman, who added the nitrate salt of the base to concentrated sulfuric acid (26JCS2912;

29JCS549). Interest has lain in whether pyridines nitrate as the free base or as the pyridinium ion (72CC641), and also the effect of steric, as well as electronic, factors on controlling the direction of substitution. Biphenyl gives principally *ortho/para* substitution, and a very high *ortho:para* ratio at low contraction in 50–70% sulfuric acid, for unknown reasons [71JCS(B)2443; 72TL1755]. The effect of using nitric acid: acetic anhydride in comparison with reactions with standard aromatic compounds is also of interest [71JCS(B)2461].

Hands and Katritzky (58JCS1754) compared the nitration of the phenyl and benzylpyridines and their *N*-oxides. The results are shown in Table VIII. The tentative conclusion was that 2-phenylpyridine and its *N*-oxide nitrated as the free base, but that benzylpyridines may be nitrated as conjugate acids. However, later work has shown that, in fact, both compounds react as their conjugate acids [68JCS(B)862]. Further work has shown that the same result occurs with 4-phenyl and 4-benzylpyridines [71JCS(B)712].

In the case of 2-phenyl-3-pyridinols, nitration in mixed acid (nitric acid *d* 1.34) at 0°C (2–3 h), gave 2-(4-nitrophenyl)-3-pyridinol (88%), but another compound (8%) was obtained whose structure was not identified (70IZV1897). In contrast the nitration of 3-phenyl-2-pyridone using mixed acid has given only the *meta* nitro isomer (99%) (85M11). If the phenyl ring of the pyridinol has a 4-substituent, then about 90% of the (3-nitro-4-*x*-phenyl)-3-pyridinol is obtained. On further nitration the pyridine ring is attacked to give, for example, 6-nitro-2-(3-nitro-4-methylphenyl)-3-pyridinol (70IZV2385).

The nitration of 6-phenyl-2-pyridone (70% nitric acid or nitronium tetrafluoroborate at RT) produces 3-nitro-6-phenyl-2-pyridone (up to 60% yield). However, nitration at 90°C with 70% nitric acid is reported to give 3-nitro-6-(4-nitrophenyl)-2-pyridone (36%), whereas at 90°C acetyl nitrate yields 50% of a mixture of 3- and 5-nitro-6-phenyl-2-pyridone (72KGS1374).

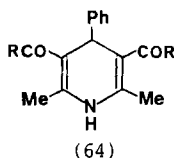
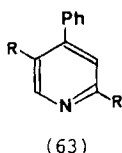
TABLE VIII
NITRATION OF SOME ARYLPYRIDINES (58JCS1754)

Compound	Yield(%)			Yield(%) for N-oxide		
	<i>ortho</i>	<i>meta</i>	<i>para</i>	<i>ortho</i>	<i>meta</i>	<i>para</i>
2-Phenylpyridine	5	35	42	12	56	6(ave. values)
3-Phenylpyridine	—	—	64	—	—	38
4-Phenylpyridine	13	28	38	12	51	13
2-Benzylpyridine	—	10	67	—	2	55
3-Benzylpyridine	—	—	63	—	(not studied)	
4-Benzylpyridine	—	5	70	—	—	9

2,5-Dimethyl-4-phenylpyridine undergoes nitration using mixed acid at 0°C (1 h) to form 25% of the 4-nitrophenyl product and 35% of a dinitro product, which has not been characterized. The corresponding acid (**63**, R = CO₂H) gives the 3-nitrophenyl product (60%) (76CHE312).

The nitration (sodium nitrite : sulfuric acid) of 4-phenyl-1,4-dihydropyridines of type (**64**) also result in 4-nitrophenyl products (56–72%) (87CHE55).

In the case of the 1-phenylpyridinium ion, an early report indicated that it nitrated at the 3-position of the phenyl ring (25CB1893), although phenyl groups attached to a nitrogen in a five-membered ring tend to be attacked at the 4-position. The nitration of 1-phenyl-4-pyridone is also reported to give the *para* product, whereas 5-methyl-1-phenyl-2-pyridone is nitrated in the 3-position (60BRP851033).



The position of nitration of the 1-phenylpyridinium ion, and that of sulfonation and bromination, has been confirmed as *meta* and has been rationalised by a MNDO analysis (86H2545).

In the case of the nitration of 2-anilinopyridine, reaction occurs with the anilino-pyridinium ion in sulfuric acid, but on the free base in acetic anhydride. The products are exclusively those of *ortho/para* substitution (72CPB2686).

1-Phenylpiperidine reacts with fuming nitric acid (*d* 1.5) at –10°C to produce about 90% 1-(2,4-dinitrophenyl)piperidine. Mononitration can be achieved by using nitric acid in acetic anhydride at RT, which gives the 4-nitrophenyl product in quantitative yield with no *ortho* product to be seen. The 4-nitrophenyl product is nitrated by concentrated nitric acid (*d* 1.42) to give the 2,4-dinitrophenyl compound, but the 2-nitrophenyl isomer (prepared from piperidine and 2-nitrochlorobenzene) is unaffected even by fuming nitric acid (32JCS1376).

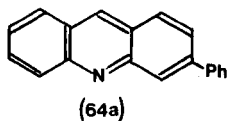
Although there are several studies of the reactions of quinolines, there is a paucity of data on electrophilic substitutions. In the case of quinoline, with the exception of the 5-position, all of the others are deactivated relative to benzene, but only by a slight amount [71JCS(B)4, 71JCS(B)2382]. The partial rate factors for quinoline have also been determined [71JCS(B)1254].

The nitration of 2-phenylquinoline with fuming nitric acid (*d* 1.5) at 0°C gives the 4-nitrophenyl derivative (66%) and the 3-nitrophenyl derivative (33%) with no *ortho* isomer being isolated. However, nitration of 2-phenylquinolinium methosulfate gives a quantitative yield of the 3-nitrophenyl product (30JCS2236). The nitration of 2-phenylquinoline-1-oxide, using potassium nitrate in sulfuric acid, is dependent on the strength of the acid. Reaction in concentrated sulfuric acid gives the 3-nitrophenyl isomer as the only isolated product, whereas the use of 70–75% sulfuric acid gives mainly the 4-nitroquinoline product with some 3-nitrophenyl product. Further nitration of both compounds gives the same 4-nitro-2-(3-nitrophenyl) dinitro product (77CPBI256).

Mononitration of 3-phenylquinoline (mixed acid) yields 3-(4nitrophenyl)quinoline as the only isolable product (64%). Further nitration gives two products, the main one is 5-nitro-3-(4-nitrophenyl)quinoline (65%), also obtained by the nitration of 5-nitro-3-phenylquinoline, and the second (10%) was not established (58JOC271). 4-Phenylquinoline yields the 2-, 3-, and 4-nitrophenyl products in the ratio 60 : 30 : 5 (1887CB624).

The nitration of 2-phenylquinoline-8-carboxylic acid using fuming nitric acid is reported to give a mixture of mononitro products from which the 4-nitrophenyl compound is crystallized (89JMC396).

The situation regarding the nitration of acridines seems to be unclear. It has been said that nitration and chlorination of 9-phenylacridine (**64a**)

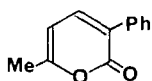


give 3,6-disubstituted products but that sulfuric acid and the other halogens attack the phenyl ring (06CB977; 66MI1). Di- and trinitro derivatives (unspecified) have been obtained by "direct substitution" (1884LA1).

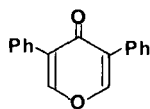
9-Benzylacridine has been confirmed to produce 9-(4-nitrobenzyl)acridine (48JOC674).

B. PYRAN, PYRYLIUM SALTS, ETC.

Both nitration and halogenation of 6-methyl-3-phenylpyran-2-one (**65**) are reported to give 4-(substituted)phenyl products (85CHE1215), whereas 3,5-diphenyl-4-pyranone (**66**) is nitrated under slightly different conditions to yield *ortho* and/or *para* di- and tetranitrophenyl derivatives. 2,6-Diphenyl-4-pyranone in contrast undergoes *meta* nitration (85JHC1333).



(65)

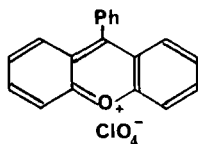


(66)

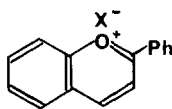
The action of nitric acid and sulfuric acids on 2,6-dimethyl-4-phenylpyrylium sulfoacetate produces a mixture of *ortho*, *meta*, and *para* nitrophenyl products in the ratios 17 : 64 : 19, respectively (89RRC1449).

2,4,6-Triphenylpyrylium perchlorate reacts with fuming nitric acid at 0°C to produce a tris(nitrophenyl) derivative in which the 2- and 6-phenyl groups are nitrated in the 3-position and the 4-phenyl group is nitrated in the 4-position. The positions of the nitration were established by nitration of the unambiguously synthesized mononitro derivatives (32JCS2894).

9-Phenylxanthylum perchlorate (**67**) is nitrated to give the 3-nitrophenyl product in almost quantitative yield (51JA891), and 2-phenylbenzo pyrylium ferrichloride and perchlorate (**68**) are nitrated, using mixed acid at 15°C, to give the 3-nitrophenyl product in yields up to 86% (29JCS2771).



(67)



(68)

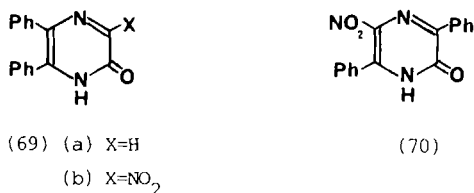
C. DIAZINES AND FUSED SYSTEMS

1. Pyridazines and Pyrazines

There are few reports of the nitration of the pyridazines and pyrazines. The nitration of phenylpyridazines has been stated to occur exclusively in the phenyl ring (73MI1). The use of fuming nitric acid at 0°C forms only the 4-nitrophenyl derivative (95%), as does 4-chloro-2-phenyl-3-pyridazone (100%), and 4-amino-2-phenyl-3-pyridazone (60%) (47JCS549).

In the case of the pyrazines it was originally thought that they were resistant to nitration and that arylpyrazines would only nitrate in the aryl ring (1888CB1269; 53JA5517). However, it was shown that the nitration of 5,6-diphenyl-2-pyrazinone (**69**), using nitric acid (*d* 1.5) in acetic acid at 25°C yields the 3-nitropyrazine product (69%) without any phenyl ring attack. The nitration of 3,6-diphenyl-2-pyrazinone has not been fully eluci-

dated, although there are several reports of the reaction (1899CB2206; 27JCS692; 49JCS910; 53JA5517). It was proposed, but not established, that nitration occurred in the phenyl ring in this case, but it was later shown that nitric acid in acetic acid converts this compound to 5-nitro-3,6-diphenyl-2-pyrazinone (**70**) (75%). 3-Phenyl-2-pyrazinone also gives a 5-nitropyrazine product under these conditions without phenyl ring substitution. Bromination of phenylpyrazinones also occurs in the pyrazine ring (56JA4071).



The simple phenyl-substituted pyrazines do undergo nitration in the phenyl ring; for example, 2-phenylpyrazine yields the 4-nitrophenyl derivative (mixed acid), although 5-phenyl-2-pyrazinone forms the 3-nitropyrazinone under similar conditions (75M11). However, 2,5-dimethyl-3,6-diphenylpyrazine and its *N,N'*-dioxide are both reported to be nitrated to give the bis-(3-nitrophenyl) products (55JCS3094).

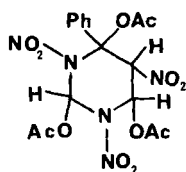
2. Pyrimidines

The first nitrations of 2- and 4-phenyl pyrimidines using mixed acid gave only the 3-nitrophenyl isomers as the isolated products (80% and "moderate yield," respectively) (51JCS2323). The nitration of 4,6-dimethyl-2-phenylpyrimidine also yields the 3-nitrophenyl product (51JCS2323; 91UP1), confirmed by independent synthesis, and not the 5-nitropyrimidine product as first reported (39JPJ462). The nitration of 5-acetylamino-2-phenylpyrimidine and 5-nitro-2-phenylpyrimidine has also been reported to give the 3-nitrophenyl derivatives (30 and 40%, respectively) as the only isolable products [68JCS(C)836].

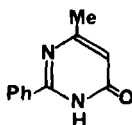
However, later work has shown that the situation is not so straightforward. Lynch and Poon (67CJC1431) studied the nitration of 4-phenylpyrimidine using three different methods: (a) nitric acid : sulfuric acid, (b) nitric acid : acetic anhydride, and (c) nitric acid : trifluoroacetic anhydride. Reagent (b) does not effect nitration in the phenyl ring but gives the product (**71**). The nitration using mixed acid gives 4-(2-nitrophenyl) and 4-(3-nitrophenyl)pyrimidine in the ratio 2 : 3 with no 4-nitrophenyl

product being detected. Reagent (c) gave the 2-, 3-, and 4-nitrophenyl products in the ratio 45 : 29 : 26.

Other workers confirmed the above results but did not isolate any of the 4-nitrophenyl product. The nitration of 5-bromo and 5-chloro-2-phenylpyrimidine was also shown to yield the *ortho* and *meta* products (in the ratio of about 3 : 7) with no *para* isomer being observed (80H1989). Further work has indicated that 5-nitro-2-phenylpyrimidine undergoes nitration in mixed acid at 0°C to give a similar mixture of *ortho* and *meta* products (1 : 7) with no *para* isomer, whereas 6-methyl-2-phenylpyrimidin-4-one (72) forms only a 3-nitro phenyl product (91UP1).



(71)



(72)

These results seem to indicate that there are two pathways leading to the nitro products for the 2- and 4-phenylpyrimidines. Nitration of the free base, or of the protonated heterocycle, leads to *meta* nitration. However, if an *N*-nitro intermediate is formed, which can undergo intramolecular nitration in a solvent cage, then *ortho* attack results (Fig. 12).

The possibility of such a process occurring in other heterocycles has been considered, but so far no other cases of this *ortho/meta* direction have been observed.

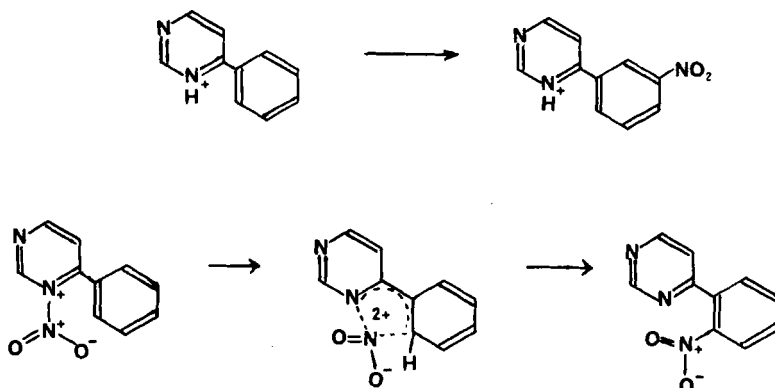
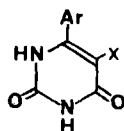


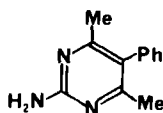
FIG. 12.

The nitration of 6-phenyluracil (**73a**) using fuming nitric acid in acetic acid:acetic anhydride is reported to give the 5-nitropyrimidine product, but the use of fuming nitric acid in sulfuric acid also yields 6-(3-nitrophenyl)-5-nitrouracil (**73b**), and other products [71JCS(C)1945]. The use of fuming nitric acid at 10°C produces 6-(4-nitrophenyl)uracil [69JCS(C)1883].

No quantitative or systematic studies of the nitration of 5-phenylpyrimidines seem to have been carried out, but a number of preparative reactions have been recorded. In each case, except that of 2-amino-4,6-dimethyl-5-phenylpyrimidine (**74**), which gives mainly the 3-nitrophenyl derivative, the principal nitration product is the 4-nitrophenyl derivative. The results that have been obtained are given in Table IX.



(73) (a) $\text{Ar}=\text{C}_6\text{H}_5$
(b) $\text{Ar}=3\text{-NO}_2\text{C}_6\text{H}_4$

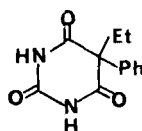


(74)

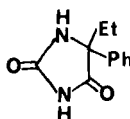
TABLE IX
NITRATION OF 5-PHENYLPYRIMIDINES AND 5-PHENYLPYRIMIDINONES

				Products(%)			Reference
R	R ¹	X	Method	<i>o</i> -	<i>m</i> -	<i>p</i> -	
Me	Me	NH ₂	KNO ₃ /H ₂ SO ₄ , RT	—	42	"Some"	71JCS(C)250
Me	Me	OH	KNO ₃ /H ₂ SO ₄ , RT	—	—	24	71JCS(C)250
H	H	NH ₂	KNO ₃ /H ₂ SO ₄ , RT	—	—	80	71JCS(C)425
H	H	MeSO ₂	KNO ₃ /H ₂ SO ₄ , RT	—	—	82	71JCS(C)425
H	H	OH	KNO ₃ /H ₂ SO ₄ , RT	—	—	80	70JCS(C)214
H	H	MeO	KNO ₃ /H ₂ SO ₄ , RT	—	—	81	70JCS(C)214
H	OH	H	KNO ₃ /H ₂ SO ₄ , RT	—	—	83	70JCS(C)214
H	MeO	H	KNO ₃ /H ₂ SO ₄ , RT	—	—	89	70JCS(C)214
	(i)		KNO ₃ /H ₂ SO ₄ , RT	—	—	80	70JCS(C)214
	(ii)		KNO ₃ /H ₂ SO ₄ , RT	—	—	100	70JCS(C)214
H	OH	NH ₂	KNO ₃ /H ₂ SO ₄ , RT	—	—	80	66MII

The nitration of 5-phenylbarbituric acids also results in 4-nitrophenyl products; for example, phenobarbital (**75**) is reported to give *para* substitution exclusively (nitronium tetrafluoroborate) (86MI1). At elevated temperatures three dinitro derivatives have been isolated, including the 3,4-dinitrophenyl derivative (77AP326). The related compound 5-ethyl-5-phenylhydantoin (**76**) also undergoes *para* nitration, whereas methyl phenobarbital gives *para* nitration but with some loss of methyl group (78AP421).



(75)



(76)

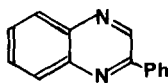
However, in contrast to these results, it has also been reported that phenobarbital yields 3-nitrophenyl derivatives as the major products and the presence of 4-nitrophenyl isomers "could be demonstrated from spectral data" but could not be isolated. The nitration of methyl phenobarbital was reported to form the 4-nitrophenyl derivative and the "formation of the 2-nitrophenyl isomer was demonstrated" (75MI2). Another early reference quotes that phenobarbital nitrates give the 3-nitrophenyl product (33JA2817; 33JA3895).

3. Benzodiazines

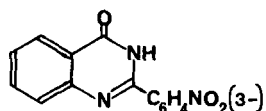
There are few reports of the nitration of phenylbenzodiazines. The nitration of 3-methyl-4-phenylcinnoline-1-oxide (**77**) with mixed acid at -10°C is stated to yield four mononitro products with no evidence for dinitration. However, the structures of these products were not established (47JCS1649). 2-Phenylquinoxaline (**78**) is reported to give the 4-nitrophenyl product (51G451). 4-Chloro-2-phenylquinazoline reacts with mixed acid at 0°C to yield the 3-nitrophenyl derivative with concomitant loss of the chloro group so that the product that is isolated is compound (**79**) (91UP1).



(77)

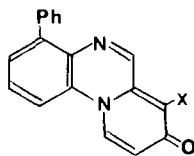


(78)



(79)

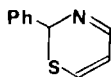
The nitration of 10-phenylglucuzidone (**80a**) has been reported to give a mononitro derivative "probably the 3-nitro derivative" (**80b**), although substitution at C-1 is not excluded (37CB1857).



(80) (a) X=H

(b) X=NO₂

In the cases of nonaromatic six-membered ring systems, several products have been observed. *N*-Phenylmorpholine is nitrated in mixed acids at 0°C to give a mixture of 3- and 4-nitrophenyl products in the approximate ratio of 5:1 (88H371). Both *N*-phenylmorpholine and *N*-phenylthiomorpholine are nitrosated to yield the 4-nitrosophenyl derivatives (21JA2233; 44JGU312). However, 2-phenyl-dihydro-1,3-thiazine (**81**) gives only the 3-nitrophenyl isomer (37JA2260).

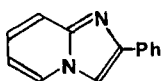


(81)

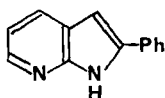
4. Imidazopyridines, Pyrrolopyridines, and Related Compounds (Azaindolizines)

A 1970 study of the nitration of 2-phenylimidazo[1,2-*a*]pyridine (**82**) indicated that it reacted first in the phenyl ring, then at C-3 (70G110, 70G1106). However, a later study, using 72% nitric in TFA, gave the 3-nitro product (with some 3-nitroso derivative) without phenyl ring substitution (83ZOR1558). Nitrosation and bromination also result in 3-substitution (36M11).

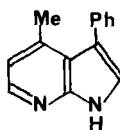
2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**83**) yields 3-nitro-2-(4-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine with fuming nitric acid at low temperature, but the use of concentrated nitric acid under similar conditions gives only the 3-nitro-2-phenyl product. Nitration of 4-methyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**84**) with fuming nitric acid produces 4-methyl-2-nitro-3-(4-nitrophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine, and in concentrated acid, a mixture of mononitro compounds is obtained. This is the first



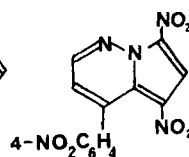
(82)



(83)



(84)



(85)

example of electrophilic substitution at the 2-position of the pyrrolo[2,3-*b*]pyridine system [69JCS(C)1505].

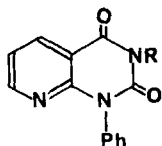
4-Phenylpyrrolo[1,2-*b*]pyridazine readily undergoes nitration to yield the trinitro derivative (85)(71JHC1).

In general the phenylazaindolizines that have a phenyl substituent are nitrated in the 4-position of the phenyl ring, and this is favored over substitution in the heterocyclic nucleus (70G110).

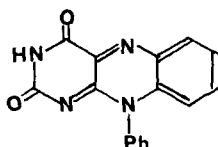
5. Pyrimidines with Fused Rings

The pyridopyrimidines (86) react with nitric acid in sulfuric acid to give high yields of solely the 3-nitrophenyl derivatives [75JAP(K)82066], whereas the only reported example of the nitration of a phenylpteridine (10-phenylflavin, 87) uses fuming nitric acid in sulfuric acid and yields the 3-nitrophenyl product, but in a poor yield(34%)(91JMC1818).

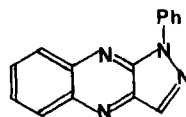
In contrast the nitration of 1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (88) results in a mixture of isomers with the 4-nitrophenyl isomer being the principal product (73ZC11).



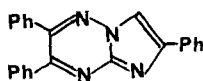
(86)



(87)



(88)



(89)

6. Triazines and Fused Systems

The nitration of 2,4-diamino-6-phenyl-1,3,5-triazine gives the 3-nitrophenyl product. Anilino-phenyltriazines undergo substitution in the aniline ring (4- and 3-) then in the phenyl ring, at the 4-position (74M11). The nitration of 2,4,6-triphenyl-1,3,5-triazine in fuming nitric acid was presumed to give the tris-3-nitrophenyl product (1860LA23; 1895JPR399; 41JCS278). However, a claim was made that the product was not the tris-3-nitrophenyl derivative (39GEP682391), although more recent work has confirmed the original result (91UP1).

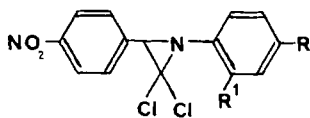
The 2,3,6-triphenylimidazo[1,2-*b*]triazines (**89**) undergo nitration, and other electrophilic substitutions, at C-7 (84CHE335).

IV. Miscellaneous Ring Systems

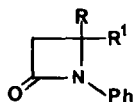
A. SMALL RINGS

Nitrations of phenyl derivatives of small ring heterocycles have been little studied. The nitration of 3-(4-nitrophenyl)-1-phenyl-2,2-dichloroaziridine (**90**) using potassium nitrate in sulfuric and acetic acids yields 1,3-bis(4-nitrophenyl)-2,2-dichloroaziridine and 3-(4-nitrophenyl)-1-(2-nitrophenyl)-2,2-dichloroaziridine in 65 : 35 ratio. Under the same conditions the diphenyl derivative undergoes cleavage of the aziridine ring to give a mixture of nitrated anilides.

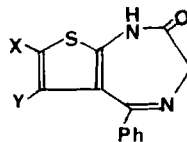
The nitration of phenylazetidiones (**91**) with acetyl nitrate gives *ortho* and *para* nitrophenyl products with no *meta* products being observed. The *ortho* : *meta* : *para* ratio depends on the substituents. However, these results were not fully quantitative and may not be complete (85ACH191).



(90)



(91)



(92) (a) X=Cl, Y=H

(b) X=Cl, Y=NO₂

(c) X=Y=H

B. LARGE RINGS

There are also few reports of the nitration of phenyl derivatives of large ring heterocycles. 7-Chloro-5-phenyl-1*H*-thieno[2,3-*e*]-1,4-diazepin-2(3*H*)-one (**92a**) is nitrated to yield the 6-nitro derivative (**92b**) without phenyl substitution. 5-Phenyl-1-*H*-thieno[2,3-*e*]-1,4-diazepin-2(3*H*)-one (**91c**) undergoes both nitration and chlorination to give 7-substituted products also without the formation of nitrophenyl derivatives (73M704, 73M709).

V. Conclusion

Nitrations of aromatic compounds represent one of the most important classes of organic reactions. However, although a lot of data has been collected in relation to simple substituted benzenes, and the reactions have been subjected to quantitative and theoretical studies, the nitration of phenyl heterocycles has been much less studied in a systematic way. This chapter has attempted to bring together as much information as possible on the topic through a manual search of Chemical Abstracts and recent literature.

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Halogenation of Heterocycles: II. Six- and Seven-Membered Rings

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I. Introduction

This chapter is the second of a three-part series reviewing halogenation of aromatic heterocycles. Part 1 [93AHC(57)291] described halogenation methods and their application to five-membered systems. Part 3 will cover the benz and other fused heterocyclic compounds. Material published since 1978 is emphasized, although earlier references are included where appropriate.

II. Halogenation of Six-Membered Heterocycles

A. RINGS WITH ONE HETEROATOM

1. *Pyridines*

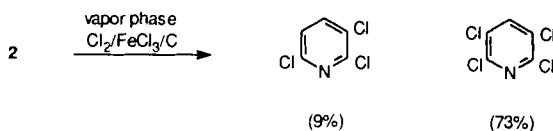
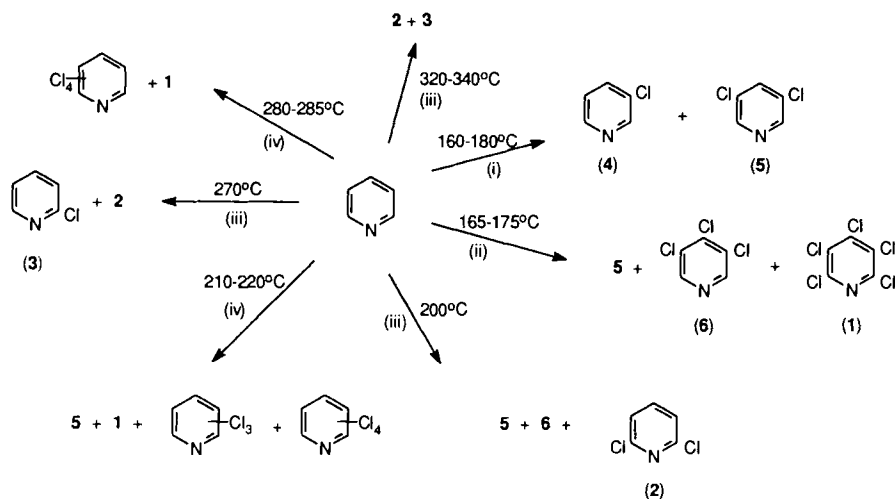
Because of the π -deficient natures of the heterorings, these compounds are reluctant to enter electrophilic substitution reactions, especially if the reagent is acidic enough to protonate the annular nitrogen. Nucleophilic halogenation processes become more important. In the benz-fused compounds electrophilic brominations preferentially occur in the homocyclic ring(s) (see Part 3). The presence of activating groups, including an *N*-oxide function, can assist some halogenation processes, although protonated *N*-oxides resemble the unoxygenated species in their reactivities. An oxide function does, however, open up the Meisenheimer reaction as a route to chlorinated derivatives.

Aspects of pyridine halogenation have been covered in a large number of review articles [61HC(14-2)299; 66AHC(6)229, 66AHC(7)1; 67MI1; 70MI1; 73MI2; 74HC(14-S2)407, 74MI2; 81AHC(28)1; 84AHC(35)281, 84MI2, 84MI3; 88AHC(44)199, 88MI2; 90AHC(47)303; 91MI2].

In pyridine itself electrophilic halogenations follow the orientation order $3 > 5 > 4$ (67MI1), whereas nucleophilic and homolytic processes favor the 2-, 4-, and 6-positions. *N*-halogenation is observed with some reagents. In some instances it is difficult to be certain of the true natures of the reacting species. Strong nucleophiles may attack ring carbons to give addition-elimination or ring-opened products; weaker nucleophiles (e.g., iodide) attack at a substituent.

a. *Chlorination.* The severe reaction conditions necessary to directly chlorinate pyridine often result in complex mixtures, but 3-chlorination is observed when conditions are conducive to electrophilic attack. As the temperature is increased, or under irradiation, the tendency for homolytic chlorination at the 2-, 4-, and 6-positions and ultimate polychlorination is increased. Among the products are aminopyridines that are formed following ring-opening of 2- and 4-pyridylpyridinium salts formed during such reactions [74HC(14-S2)407; 77HC(32-1)319]. At the higher temperatures or with ultraviolet irradiation α -chlorination precedes β -chlorination (Scheme 1).

Attempts to chlorinate pyridine selectively in the vapor phase have utilized a number of processes, including fluidized bed and turbulent flow methods to ensure good mixing, with and without catalysts. Rate coefficients have been determined for each successive chlorination step in



SCHEME 1

the formation of pentachloropyridine (1) [69USP3420833; 74MI1, 74MI2; 80JOU1845; 81JAP(K)120666, 81JAP(K)120667; 82FRP2477540; 83JAP(K)58/206564; 84GEP3306905; 87USP4701532; 89EUP300430, 89EUP311050; 90USP4939263; 91ZPK1297]. Catalysts used have included alumina, chlorides and fluorides of transition metals or carbon, and lead. Thus, vapor phase chlorination of 2,5-dichloropyridine (2) with iron(III) chloride and carbon gave a high yield of 2,3,5,6-tetrachloropyridine and some of the 2,3,6-trichloro product [83JAP(K)58/206564] (Scheme 1). In the presence of alumina at 100°C, 4-picoline was converted by chlorine into a mixture of the 3-chloro (40%) and 3,5-dichloro (15%) derivatives (80JGU354). Vapor phase chlorination at 555°C of 2,2'-bipyridine gave more than 90% of octachloro product. At lower temperatures the initial chlorination was shown to occur at the 6- and 6'-positions

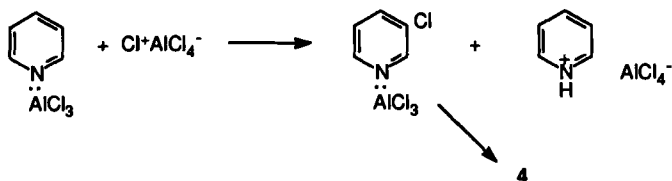
(69USP3420833). The same product was also formed using phosphorus pentachloride at 300°C [68T5633; 84AHC(35)281].

Control of the isomer distribution in the liquid phase was achieved by addition or removal of hydrogen chloride. The 5,6- : 3,6-dichloro ratio was increased by HCl addition and decreased by its removal (90USP4939263).

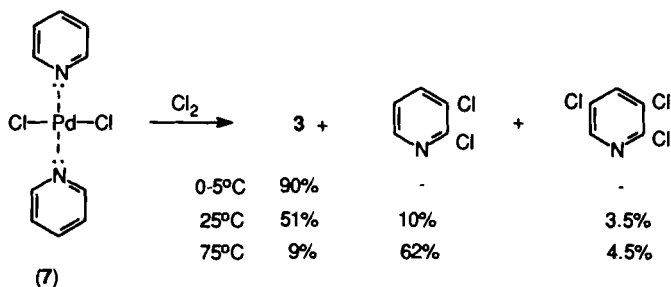
Examples in which the chlorination process is driven by ultraviolet irradiation abound, especially in the patent literature [80JGU354; 85CPB1009; 88JAP(K)63/156774; 89JAP(K)01/132564; 90USP4891108; 91JAP(K)03/236374]. For example, a 78% yield of 2-chloropyridine (3) was obtained on 15-min irradiation of pyridine in the presence of chlorine dissolved in hot aqueous carbon tetrachloride (67JHC375). The destructive chlorination of 3,4,5-trichloro-2-trichloromethylpyridine has been shown to proceed via thermal (160–245°C) and photochemical pathways, giving products in which the trichloromethyl group was replaced by chlorine. A synchronous mechanism in which a chlorine atom attacks the ring nitrogen and the 6-hydrogen was proposed as the chain-propagation step under radical conditions (85JOU1163). Under γ -irradiation conditions both nuclear and side-chain chlorination of 4-picoline were observed (80JGU354).

When gaseous chlorine was passed through a molten complex of pyridine and aluminium chloride (1 : 2) at 80–115°C, 3-chloropyridine (4) was obtained in 30–35% yield (Scheme 2). In this process the excess Lewis acid acts as a support for the positive chlorine electrophile which then reacts with the complex (another example of the “swamping catalyst effect” in which aluminium chloride is superior to ferric chloride, stannic chloride, or boron trifluoride) (61JOC789; 70USP3538100). Under analogous conditions 4-methylpyridine formed a mixture of 3-chloro (40%) and 3,5-dichloro (15%) derivatives. The pyridine–palladium(II) complex (7) reacted with chlorine to give a temperature-dependent mixture of products (80S378). (Scheme 3)

With chlorine in the presence of aluminium chloride, pyridine formed 4-pyridylpyridinium chloride; with iodine monochloride at 250°C, the 2-isomer was formed from pyridinium chloride [74HC(14-S2)407; 77HC(32-1)319]. It is well known that “positive” halogens give stable 1 : 2 salts



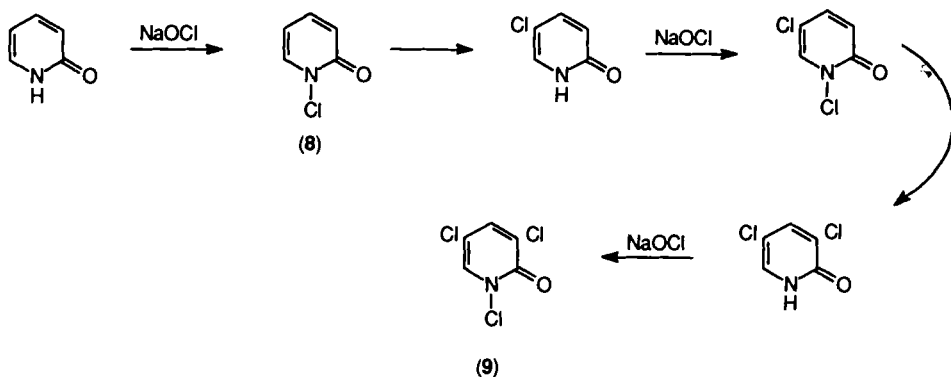
SCHEME 2



SCHEME 3

(Py_2X^+) with pyridine [74HC(14-S2)416; 86TL3271], and it is thought that the role of pyridine in steroid chlorinations may also involve a chlorine atom coordinating with the pyridine nitrogen to form a flexible complex capable of selective hydrogen abstraction from the steroid substrate (87JA7204). When 2- and 4-pyridones are treated with sodium hypochlorite unstable *N*-chloro compounds (8) are also formed, but these rapidly rearrange to give *C*-chloro products, chlorinated *ortho* and *para* to the oxygen function. The trichloro species (9) has considerable stability (84JOC4784) (Scheme 4).

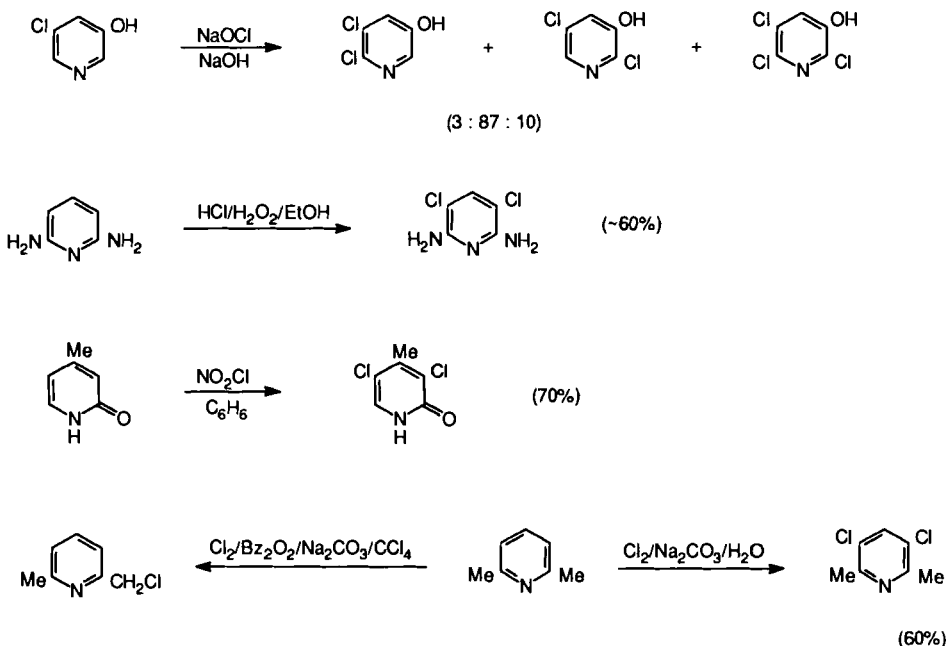
With activating groups present in the ring, pyridines can be chlorinated much more readily using reagents as diverse as sulfonyl chloride (91URP1657495), sodium hypochlorite (89SC553, 89SC1505; 90S499), calcium hypochlorite (90S499), chlorine in aqueous base (80CHE89), chlorine in acetic (90S681) or sulfuric acids (76JOC93), or with Lewis acid catalysts (83EUP78410; 86USP4594422), hydrogen chloride with an oxidizing agent



SCHEME 4

(80CC1139; 88GEP3707361; 89SC553; 90S499), and nitrosyl chloride (76M11). The chlorine usually enters positions *ortho* and *para* to the substituent. Some representative examples are shown in Scheme 5. When 2-aminopyridine was chlorinated in 17% sulfuric acid it was converted into the 5-chloro and 3,5-dichloro derivatives in almost equal amounts. In 72% acid the corresponding yields were 98 and 2%, reflecting differing chlorination rates of the free base and conjugate acid. In fact, at high acidities 5-chloropyridine is protonated, becoming resistant to further chlorination (76JOC93). Conditions can be adjusted to favor nuclear or side-chain chlorination of picolines (80CHE89; 91GEP4016175), although both frequently occur concurrently [47M11; 63AG(E)144]. Such side-chain chlorinations can be either homolytic processes or base-catalyzed reactions that may involve formation of the fully carbanionic species (e.g., 2-picoline with sodamide or butyl-lithium) [63AG(E)144].

Electrophilic chlorinations of pyridine 1-oxides are not common. Reaction of 2-acetamidopyridine 1-oxide with hydrogen chloride and hydrogen peroxide gave a mixture of 5-chloro and 3,5-dichloro derivatives; the 3-



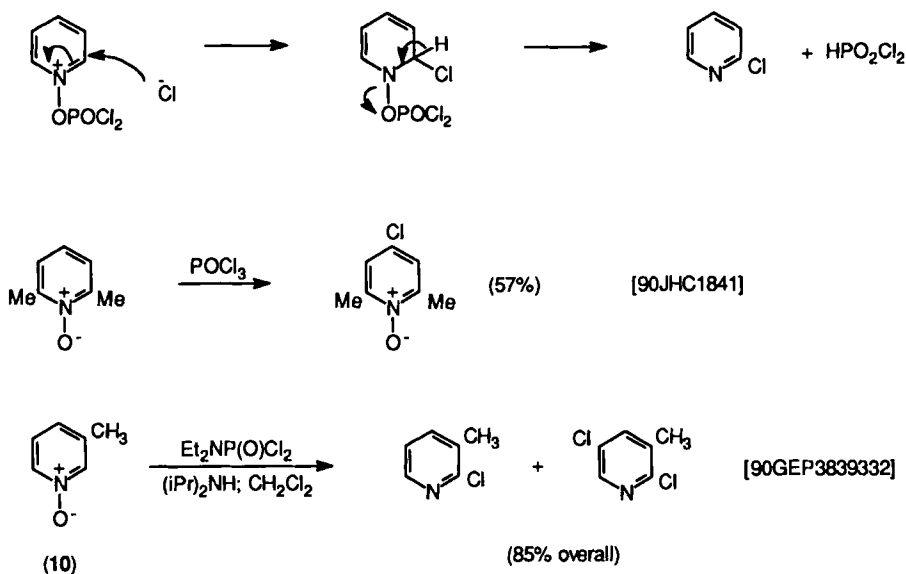
SCHEME 5

isomer gave the 2,4,6-trichloro product, whereas the 4-acetamido oxide underwent 3,5-dichlorination (83M11). Regioselective chlorination is possible if lithiated or mercurated pyridine oxides are used [88AHC(44)199]. Thus, α -lithiated pyridine 1-oxide was used to make the 2,6-dichloro derivative [72JHC1367].

Among the nucleophilic processes leading to chloropyridines the reactions of pyridones with phosphoryl or thionyl chloride have a high profile, especially for introducing chlorine to the 2-, 4-, and 6-positions (3-hydroxypyridine does not take part in this reaction) [80AG(E)388; 84S743; 85CZP219406; 87CHE865, 87CI(L)694; 88ACS(B)524; 89CPB2117; 89SC553; 90S499, 90S681]. Phosgene in formamide (83EUP72777) and phosphorus pentachloride have also been used [88ACS(B)524]. When electron donors such as methyl are present to destabilize any dihydro product, 2-hydroxy-1,4-dihydropyridines can be converted by phosphoryl chloride into 2-chloropyridines. The aromatization may be a consequence of either spontaneous air oxidation or successive chlorination and dehydrochlorination (89CPB2117). Thionyl chloride, a low boiling, recyclable liquid in comparison with phosphoryl chloride, has been recommended as an industrially preferable reagent for conversion of 2- and 4-pyridones in good yields, using solvents such as refluxing methanesulfonic acid [87CI(L)694]. An 89% yield of the 2,4-dichloro derivative resulted when ethyl 4-hydroxy-6-methyl-2-pyridone-3-carboxylate was heated at 140°C with phosphoryl chloride (88S479). Under Vilsmeier–Haack conditions 2-methoxypyridines were transformed into 2-chloropyridines in 50–71% yields (90SC2971).

Direct nucleophilic aromatic substitutions of one halogen for another are also quite common, especially when the pyridine ring contains an electron-withdrawing group, or if it is protonated or quaternized. Thus, 4-bromo-2,3,5,6-tetrachloropyridine gave **1** when treated with sodium chloride in dimethylformamide [79JCS(P1)1472]. Metal-assistance to this reaction was provided by the use of copper(I) chloride in place of the sodium chloride [80JCS(P1)1682]. The 2- and 4-bromopyridines and their *N*-oxides are more susceptible than the 3-isomers to such chloride displacement, which is best accomplished in a polar aprotic solvent [85USP4546192; 88M12].

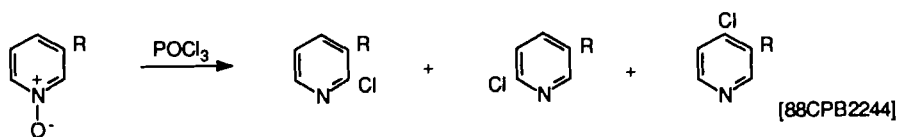
Chloride ions will not readily attack pyridine 1-oxide unless the oxygen is coordinated with such reagents as phosphoryl, sulfonyl, and tosyl chlorides; phosphorus pentachloride; or mixtures of these reagents (e.g., phosphoryl chloride–phosphorus pentachloride) [56RTC1303; 67M12; 71M11; 81JHC939; 83T291; 88CPB2244, 88S479; 90JHC1841; 92EUP46364]. Some examples of the Meisenheimer reaction are shown in Scheme 6. Attack



SCHEME 6

occurs more readily at the 2- and 6- rather than the 4-position, but substituents can modify this preference, and lateral chlorination is frequently observed. An electron-withdrawing group at C-3 increases the likelihood of 2-chlorination, although donors in the 3-position appear to be quite unspecific in their directional effects (88CPB2244) (Scheme 7). When both 2- and 6-positions were blocked by methyl the 4-chloro derivative, along with some chloromethylated products, was obtained (90JHC1841), and much the same behavior was noted with 2-methylpyridine 1-oxide.

The chlorination of methyl groups via an anhydro base can be made the exclusive reaction process (81JHC939). Whereas 4-carboxamidopyridine 1-oxide reacted with a mixture of phosphoryl chloride and phosphorus pentachloride to give the 2-chloro derivative, the corresponding 4-nitrile gave the 3-chloropyridine (78JHC683). Chlorination at the 3-position was a significant side reaction too when pyridine 1-oxide was acylaminated with *N*-phenylbenzimidoyl chloride (74JOC1795). Chlorine-containing phosphoric acid esters or amides have been recommended for the chlorination of 3-picoline 1-oxide (**(10)**) (90GEP3839332). Observed variations in product ratios with chlorinating agent (phosphorus pentachloride gives more 4- than 2-chlorination; phosphoryl chloride gives mainly 2-chloro products) could be a consequence of greater intramolecular content in the latter process.

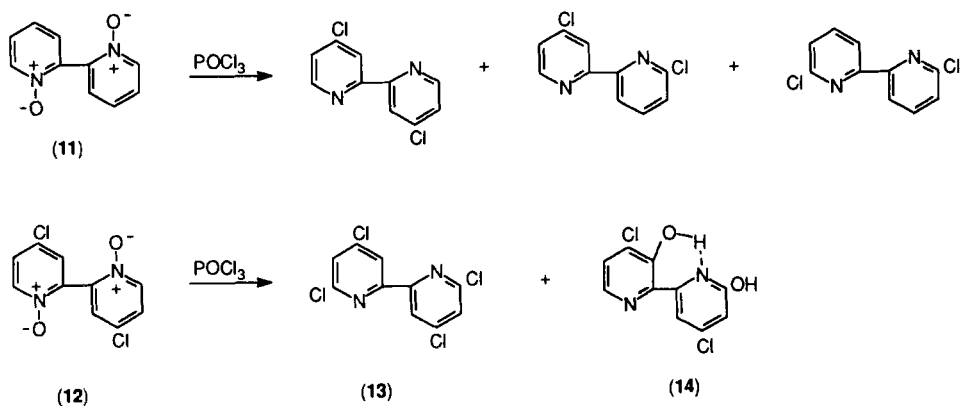


R	Ratios of Products					
H	70	:	0	:	30	
Me	30	:	27	:	43	
Ph	32	:	46	:	22	
NMe ₂	34	:	47	:	19	
CN	88	:	10	:	2	
NO ₂	73	:	27	:	0	

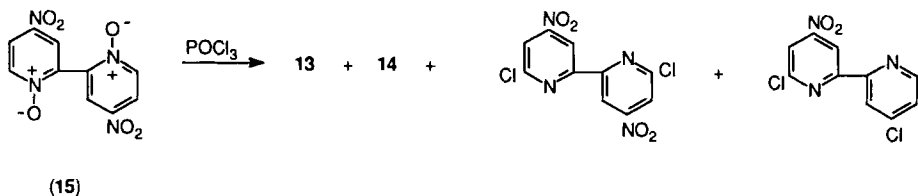
SCHEME 7

When 2,2'-bi(pyridine 1-oxide) (**11**) was heated with phosphoryl chloride, a mixture of the expected products was obtained. The 4,4'-dichloro derivative (**12**) gave mainly **13** along with a small quantity of **14**, formed as a result of attack by the *N*-oxide function on the adjacent ring (Scheme 8). In contrast, the 4,4'-dinitro compound was subject to extensive nucleophilic chlorodenitration (83T291) (Scheme 9).

Other nucleophilic chlorinations have included reactions of hydrogen chloride, phosphoryl chloride, and acetyl chloride with 4-nitropyridine 1-oxide to form 4-chloropyridine 1-oxide (86JHC177; 87MI1; 91T1697).



SCHEME 8



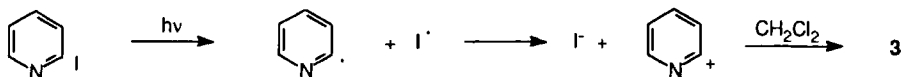
SCHEME 9

When 2-iodopyridine was exposed to ultraviolet irradiation in methylene chloride solution, 2-chloropyridine (**3**) appeared among the products, perhaps the result of an electron transfer process (85CPB1009) (Scheme 10).

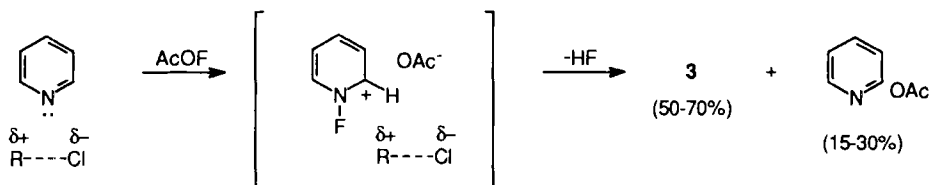
2-Chloropyridines (and other halogenopyridines) can be made by the action of acetyl hypofluorite in the presence of an appropriate alkyl halide on pyridine. The strategy employed here is to attack the basic pyridine nitrogen with a strong electrophile in order to decrease its mesomeric back donation. Electrophilic fluorine is a suitable candidate for this task. Effectively, acetyl hypofluorite "adds" across the $\text{C}=\text{N}$ bond.

In dichloromethane, pyridine formed a mixture of **3** with 2-acetoxypyridine (87TL2705; 88JOC1123) (Scheme 11). In the same way, 3-chloropyridine was converted into 2,3-dichloropyridine, and 3-benzoylpyridine gave the 2-chloro product in around 80% yields. Only traces of acetoxo products were formed, perhaps because the 2-carbocation is sufficiently stable to allow time for the acetate ion to diffuse out of the tight ion-pair cage (88JOC1123). When 1-fluoropyridinium triflate was treated with base in the presence of dichloromethane, the products included pyridine-2-triflate (21%), **3** (62%), and 2-fluoropyridine (5%). In this instance a carbene was proposed as the reactive intermediate (87TL2705). During the synthesis of 2-fluoropyridine, using cesium fluoroxysulfate with pyridine at room temperature, **3** was a by-product when the solvent was chloroform (90TL775).

Sandmeyer processes have been used more frequently to prepare other halogenopyridines. There is, however, a high yielding process for the chlorodediazotiation of pyridine diazonium fluoroborates. The 3-diazonium salt was converted into 3-chloropyridine (**4**) in 95% yield



SCHEME 10

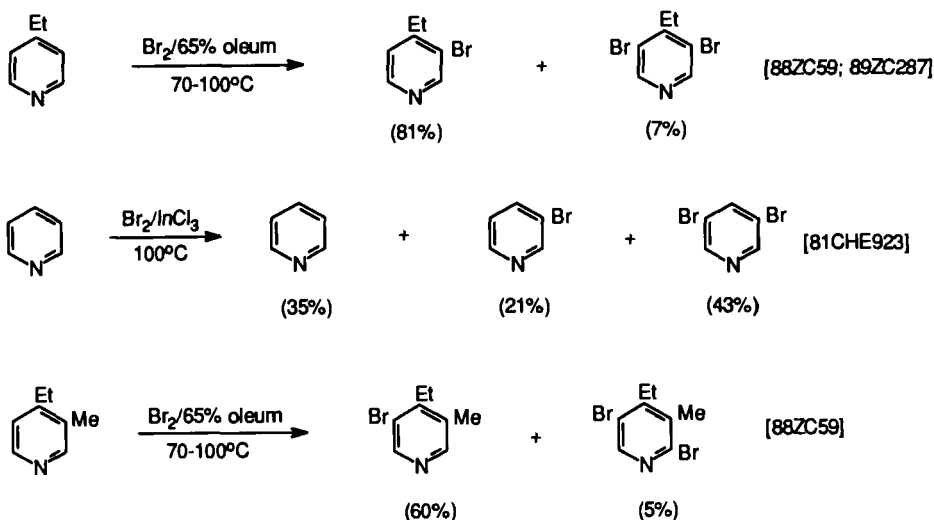


SCHEME 11

when treated with a 3 : 1 mixture of carbon tetrachloride and acetonitrile in the presence of iron(II) or iron(III) chlorides. This reaction resembles the conventional Sandmeyer process in that it involves an initial electron transfer from the reductant to the arene diazonium ion. Both 2-aminopyridine and its 4-methyl derivative reacted with dry N_2O_3 in methylene chloride in the presence of hydrogen chloride and tetrabutylammonium chloride (but in the absence of any reducing agents) to give 2-chloro products in 95% yields. Sandmeyer conditions proved less successful even in concentrated hydrochloric acid (92ACS157).

b. *Bromination.* Pyridines have been converted into 3-bromopyridines (or 5-bromopyridines) with sodium hypobromite (90S497, 90S499), with hypobromous acid in aqueous perchloric acid (74JOC3481), with bromine in aqueous solution (82JA4142; 90S499), in the vapor phase (67JHC377, 67MI1), in acetic acid [81JAP(K)128759; 85CHE1399; 86JHC1849; 90S681], in aqueous sulfuric acid [70JCS(B)117] or oleum (where the oleum oxidizes the HBr formed) (62RTC864; 65RTC951; 70RC779; 88ZC59; 89ZC287), with bromine with Lewis acids (61JOC789; 66CJC1765; 81CHE923; 88JOC5545; 89BRP2213478), with the palladium(II) complex of pyridine (80S378), with bromine monofluoride [88JOC1123, 88JOC5545], with NBS in carbon tetrachloride [76JOC2065; 82CHE1284; 90H(31)523], with bromides in the presence of oxidizing agents (80CC1139), with dioxan dibromide (82CHE1284), and with 2,4,4,6-tetrabromocyclohexa-2,5-dienone [73JCS(P1)68]. Some examples are shown in Scheme 12.

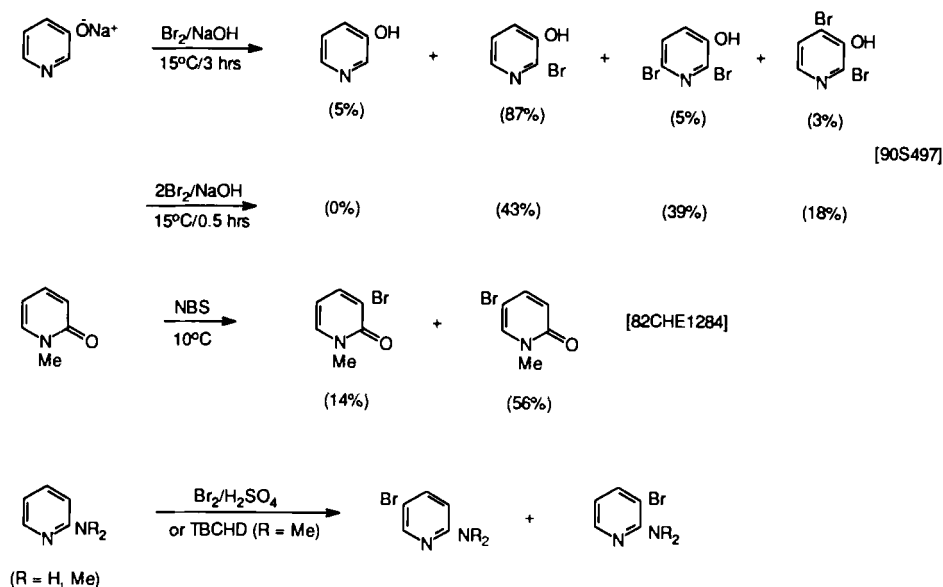
As long as activating groups are present, bromination with bromine solutions gives satisfactory results, but selective monobromination is not easy. With pyridine itself, or with weakly activated substrates such as the picolines and 2-methoxypyridine, much more forcing conditions are necessary (83JOC1064; 88ZC59; 89ZC287). Substitution usually occurs at the 3- or 5-positions unless they are blocked when 2(6)-bromination may be observed (89ZC287). The use of bromine in oleum is believed to involve



SCHEME 12

a pyridine–sulfur trioxide coordination compound ($\text{C}_5\text{H}_5\text{N}^+\text{SO}_3^-$) that reacts with bromonium ion, a process that is similar to bromination in the presence of excess Lewis acid catalysts (see below). Certainly bromination in oleum has been used frequently, and it occurs more readily as the degree of methyl substitution on the heterocycle increases (62RTC864; 65RTC951; 72BSF2466).

When bromine is used with excess aluminium chloride the “swamping catalyst effect” (see A,1,a) assists the formation of bromopyridines. Good yields of 5-bromo-3-methylpyridines (85%), 5-bromo-2-methylpyridines (40%), and 3-bromo-4-methylpyridines (32%) were obtained by use of this technique (61JOC789; 66CJC1765). Salts of heavy metals (Hg, In) have proved particularly useful and provide substantial back-donation from their complexes with pyridines; even with aluminium chloride about 15% 3-bromination of pyridine was achieved. Higher temperatures can improve yields, but some complexes are thermally unstable (81CHE923). A change in orientation was observed with the palladium(II)–pyridine complex, which gave an 86% yield of 2-bromopyridine and only about 10% of the 3-isomer (80S378). Quite clearly it becomes much easier to brominate unactivated pyridines when the molecule is complexed or when the electrophile can be made more “positive.” Thus, bromine monofluoride has proved an effective reagent. It can be prepared *in situ* by passing fluorine through a cold suspension of bromine dissolved in trichlorofluoromethane.

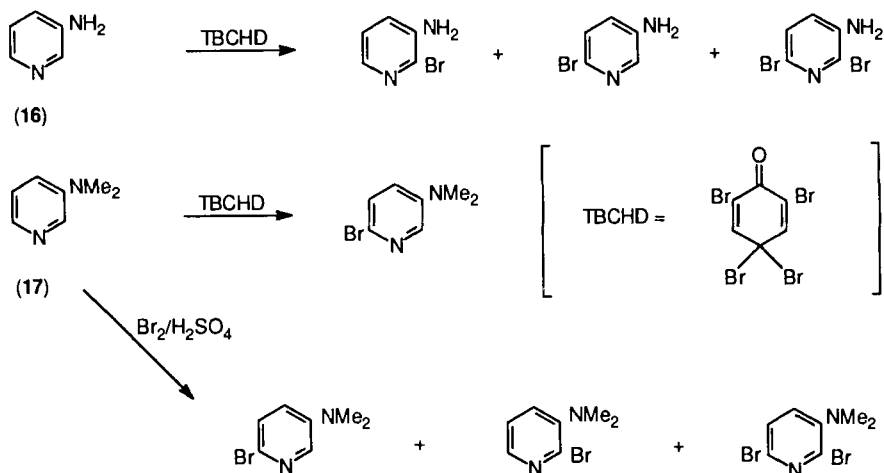


SCHEME 13

This solution is used without purification because BrF disproportionates to BrF_3 and bromine (88JOC1123, 88JOC5545).

When strongly activating groups are present, the preparation of bromopyridines by electrophilic methods becomes a much more facile operation, with the bromine being directed into positions *ortho* and *para* to the substituent (unless these sites are blocked) [50RTC1281; 70JCS(B)117; 73JCS(P1)68; 82CHE1284, 82JA4142; 89JPR369; 90S497, 90S499] (Scheme 13). Sometimes a change in brominating agent can induce a change in regiochemistry. Both 2-amino- and 2-dimethylamino-pyridines gave 5-bromo products when treated either with bromine in sulfuric acid or with the sterically demanding 2,4,4,6-tetrabromocyclohexa-2,5-dienone. The 3-amino isomer (**16**) gave a mixture of 2-, 6-, and 2,6-di-bromo products, but the corresponding dimethylamino compound (**17**) gave only the 6-bromo derivative [73JCS(P1)68] (Scheme 14).

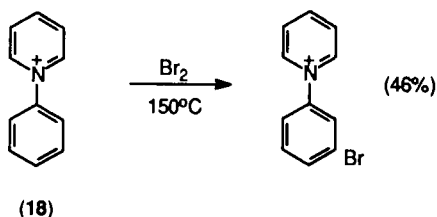
3-Hydroxypyridines react very much like phenols; they are not subject to keto-enol tautomerism to a significant degree. In aqueous alkali the oxyanion is the reactive species with bromine entering positions *ortho* and *para* to that substituent. It has proved possible to achieve a high proportion of monobromination by the use of one molar equivalent of bromine. As the proportion of bromine to substrate was increased more



SCHEME 14

dibromination eventuated, but there was no sign of any 4-bromination (90S497) (Scheme 9). Previously, a 50% yield of 2,4,6-tribromo-3-hydroxypyridine had been reported on aqueous bromination of 3-hydroxypyridine (50RTC1281). The 2- and 4-pyridones also brominate very readily in positions *ortho* and *para* to the oxy function. These reactions will be discussed in more detail below.

Mechanisms of pyridine bromination have been intensively studied. When methylpyridines are treated with hypobromous acid in perchloric acid the conjugate acids are involved (74JOC3481). The partial rate factor for pyridinium bromination ($2-6 \times 10^{-13}$) compared with those estimated for the bromination of methylpyridinium species indicates that methyl groups accelerate the reaction. A 2-methoxy group has an effect roughly equivalent to three methyl groups at positions-2, -4, and -6, whereas 2,6-dimethoxypyridinium brominates at around 4×10^4 the rate of 2-methoxypyridinium. When the 3- and 5-positions are not equivalent as in 2-methoxypyridinium the more reactive center is that adjacent to the alkyl substituent (74JOC3481). Pyridine is, in fact, not brominated in 77.5% perchloric acid at 25°C, and so the above partial rate factor is an estimated value. The difficulty of brominating the pyridinium species is exemplified by the high-temperature bromination of 1-arylpyridinium salts (18), which were substituted mainly in the *meta* position of the phenyl group (Scheme 15). This contrast with the usual *para* substitution observed with *N*-aryl-heterocycles, and the above behavior has been rationalized in terms of an MNDO analysis, which took into account the near degener-

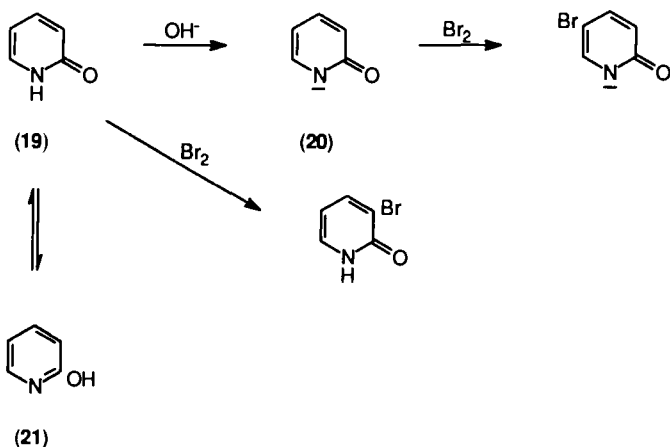


SCHEME 15

acy of the two top HOMOs, and which used experimentally probable angles between the rings [86H(24)2545].

Kinetic studies of the bromination of 2-aminopyridines and their 5-substituted derivatives (Me, Cl, Br, NO_2) using solutions of bromine in dilute sulfuric acid have demonstrated that the minority free base species react with molecular bromine at 25°C and that the usual substituent effects on rates apply [70JCS(B)117; 78APO(16)1].

Below pH 6, 2-pyridone (19) is brominated in aqueous solution as the neutral species, preferentially in the 3-position. Above pH 6, the conjugate anion (20) is brominated mainly at C-5. At low pH, the hydroxy tautomer (21) has been shown to be at least 2000 times less reactive than 19. *N*-Methylpyridones are not particularly reactive above pH 6 because they cannot form the anions. The 5-bromo derivatives of 19 behave similarly except that 5-bromo-2-pyridone is much more reactive than its *N*-methyl derivative above pH 4. This is in accord with the lower pK_a value of the bromo compound [82JA4142; 90AHC(47)303] (Scheme 16).



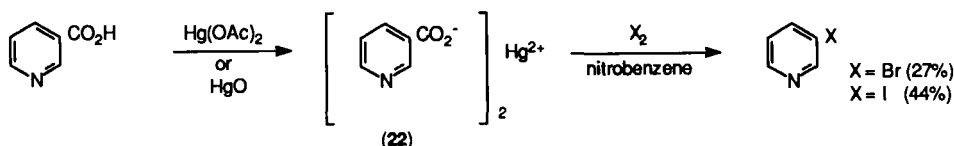
SCHEME 16

The 4-pyridones behave similarly, with the neutral tautomer reacting below pH 6 and the anion at higher pH. The observation that 4-methoxy-pyridine shows little comparative reactivity over the whole range is evidence that the hydroxy tautomer is not involved in the bromination process. Again, once the first bromine has entered the ring, further bromination occurs more readily because of easier anion formation (83CJC2556).

Monobromination of these oxy compounds is difficult to achieve even at low temperatures and with low molar proportions of bromine. At -10°C , bromine converted 1-methyl-2-pyridone into a mixture of 3- and 5-bromo derivatives (1 : 2), but with 18% 3,5-dibromination as well. Reagents such as NBS at 10°C and dioxan dibromide were more effective giving a 1 : 4 ratio of 3- : 5-bromo in a total yield of 56%, and a 1 : 1.3 ratio (with 8% dibromination) in a total yield of 81%, respectively (82CHE1284).

Even in the presence of electron-withdrawing substituents, bromination is frequently possible. A high yield of 3-bromo product was obtained on aqueous bromination of 5-nitro-2-pyridone (90S499), and bromine in chloroform gave an 80% yield of the 5-bromo derivative of 2,6-dimethylthio-4-phenylpyridine-3-nitrile (84EGP205895). Bromine in acetic acid converted dihydropyridylidenecyanoacetic esters into the 5-bromo derivatives (70–80%) (85CHE1399). Bromine in nitrobenzene gave the 3-bromo derivative (27%) of mercury(II) nicotinate (**22**) (Scheme 17). This reaction also works with thallium salts, but the mercury(II) nicotinates are about three times better. The process is believed to involve an initial ionic pathway in which the electrophilic mercury(II) species attacks the ring carbon bearing the carboxyl group to give a 3-pyridylmercury compound. Subsequent electrophilic displacement of this group (with bromine or iodine) then occurs (83JOC3297).

Despite the array of brominating agents available, polybromination of pyridines has proved difficult. The usual products are 3-bromo or 3,5-dibromo derivatives [88AX(C)1800] with even dibromocyanuric acid being relatively ineffective (68M815). In consequence, there have been a number of attempts to apply vapor phase bromination to pyridine, using elevated temperatures to induce homolytic reactions. Substitution patterns can be



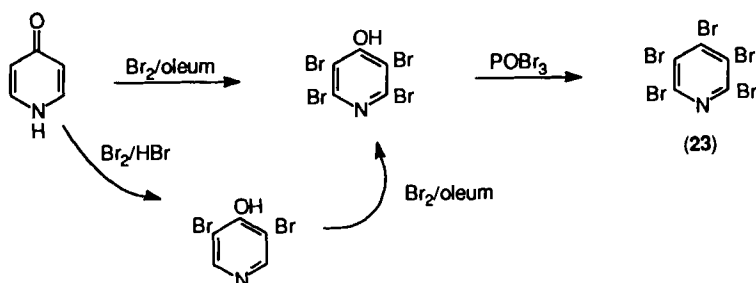
SCHEME 17

varied by changing the contact packing. For example, at 450–550°C in the presence of pumice, pyridine mainly gave 2,6-dibromopyridine; with pumice and ferric bromide a mixture of 2,3,5-tri- and 2,3,5,6-tetrabromopyridines eventuated (58RTC66). Nucleophilic substitution by bromide on pentachloropyridine was also of limited use [76HCA229; 79JCS(P1)1472]. Seemingly the best method of preparation of pentabromopyridine (**23**) used the reactive 4-pyridone, and then replaced the oxygen function at the final stage [56AP651; 78CHE55; 88AX(C)1800] (Scheme 18).

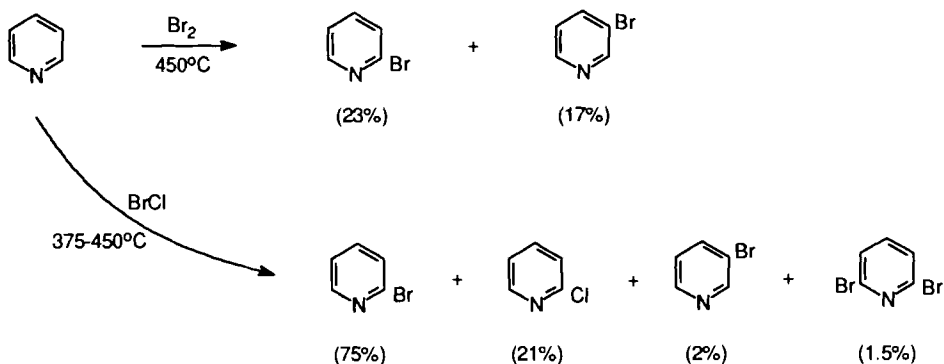
Vapor phase brominations have, however, proved useful and interesting because of the obvious mechanism change from electrophilic to homolytic as the temperature increases (67MI1). At 300°C pyridine was converted mainly into a mixture of 3-bromo and 3,5-dibromo products; at 500°C the products were 2- and 2,6-dibromo derivatives. Mixtures of these were obtained at intermediate temperatures (67JHC377). The facility with which pyridine reacts with NBS also suggests some radical involvement [82CHE1284; 90H(31)523]. Bromine monochloride seems to be an even more specific reagent than bromine for 2-bromination at high temperatures (67JHC377) (Scheme 19). Bromination of 3,3'-bipyridine at 250°C gave a 20% yield of the 5-bromo derivative [84AHC(35)281].

Pyridines react quite readily with bromine to give crystalline derivatives that have some *N*-bromo characteristics, but that are related to the tribromide anion. In nonpolar solvents the species are largely undissociated. Positive bromine gives stable 1 : 2 salts and 1 : 1 complexes with pyridine [74HC(14-S2)416; 86TL3271], but, in contrast to the chloro derivatives, *N*-bromo-2-pyridones are not known (82JA4142; 84JOC4784).

There are a few examples of the preparation of bromopyridines from metallic derivatives, and lithio- and mercurio-pyridines are readily made in high yields [72JHC1367; 74HC(14-S2)489; 82T3035; 85T3433; 88AHC(44)199]. Examples of transmetallation are known, as when lithiation of 3-bromopyridine gave the 4-bromo isomer (82T3035; 85T3433).



SCHEME 18



SCHEME 19

A 3-bromopyridine was made from the reaction of the 3-tributylstannyl derivative with NBS (87TL759).

Side-chain bromination frequently accompanies annular brominations when reagents or conditions conducive to homolytic reactions are used. When NBS in carbon tetrachloride reacted with 1,3-dimethyl-2-pyridone a 96% yield of the 5-bromo derivative resulted; with added benzoyl peroxide the product was 3-bromomethyl-1-methyl-2-pyridone (63%) (76JOC2065), and there are other examples (85CHE1399).

Electrophilic bromination of pyridine 1-oxides has been more widely studied than chlorination. Yields are frequently poor, and vary from reagent to reagent. Thus, although bromination with an iron catalyst at 110°C failed (55JA2902), 2- and 4-bromination was achieved using 90% sulfuric acid with bromine and with the bromine-sulfuric acid-silver sulfate system at 200°C. The pyridine 1-oxide free base was the reactive species (61TL32; 62T227; 71M11). When the oxide is complexed with sulfur trioxide, or when it is protonated (e.g., in oleum) the orientation of bromination reverts to that of pyridinium, the products are 3- and 5-brominated compounds (62T227). Bromination in acetic anhydride also occurred at C-3 (35%), but an addition-elimination mechanism may account for this regiochemistry (65JPJ62). When 3-bromopyridine 1-oxide was heated with bromine in 90% sulfuric acid, the 2,3-, 3,4-, and 2,5-dibromo oxides were obtained in low yield (presumably the free base is being brominated). The further observation that 2-bromopyridine 1-oxide gave a 4.5 : 1 ratio of 2,4- and 2,6-dibromo products supports this role of the oxide function in controlling regiochemistry. In oleum, however, both 2- and 4-bromopyridine 1-oxides were mainly substituted at the 3- and 5-positions, indicating that either the *N*-hydroxy cationic species or a complexed (with SO_3) species was reacting with bromine (62T227). In

the presence of thallium(III) acetate 2,6-dimethylpyridine 1-oxide was converted by bromine in acetic acid into the 4-bromo derivative (49.5%) [79H(12)475]. Strong electron donors in addition to the oxide function assist nuclear bromination (71M11), but 2- and 4-methoxy groups are not particularly activating. In 4-methoxypyridine 1-oxide, hydrolysis of the ether preceded bromination. A good yield of 5-bromo derivative was obtained on bromination of 2-dimethylaminopyridine 1-oxide (83JOC1064).

Nucleophilic approaches to bromopyridines are an attractive alternative to electrophilic methods, and they are especially valuable for making 2-, 4-, and 6-bromopyridines. Decompositions of diazonium salts with copper(I) bromide have been used frequently, leading to 2-bromopyridine (81USP4291165), whereas the ready availability of 2- and 4-pyridones and their conversion by phosphoryl bromide into the bromo derivatives have also been of value [78CHE55; 83TL2973; 88ACS(B)524; 89M1095; 90S499]. Other groups (2-nitro, 2-chloro) have been replaced by reaction with HBr [81JAP(K)115776; 83JAP(K)58/18360], and pentachloropyridine was converted by HBr in acetic acid at 110°C into 2,4,5-tribromo-3,5-dichloropyridine (76HCA229). Nucleophilic displacement of the nitro group in 4-nitropyridine 1-oxide was achieved using bromine with red phosphorus in acetic acid (87M11).

One of the most interesting recent developments has been the use of *N*-fluorinated pyridines with alkyl bromides to prepare 2-bromopyridines (see also A,1,a). Yields approach 60% with about 20% of the 2-acetate as by-product (88JOC1123; 91JOC6298). With 3-chloropyridine as the original substrate, an 80% yield of 2-bromo-3-chloropyridine resulted from this process (88JOC1123). Low basicity in the original substrate limits the generality of this process, since weakly basic pyridines do not react with the electrophilic fluorine of acetyl hypofluorite (91JOC6298).

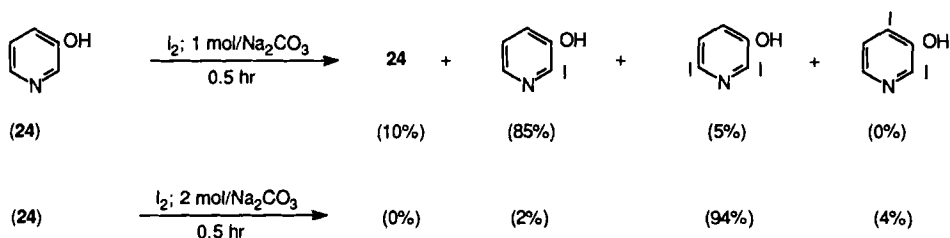
c. *Iodination.* Direct iodination of pyridine with iodine in oleum gave only 18% of 3-iodopyridine and a little of the 3,5-diiodo derivative (57JCS387). Under similar conditions 2,6-dimethylpyridine gave a 50% yield of 3-iodo derivative, and 2,4,6-trimethylpyridine formed the 3-iodo (60%) and 3,5-diiodo (5.5%) products (70RC779).

When pyridinium hydrochloride was treated at 250°C with iodine monochloride in the presence of aluminium chloride, a 2-pyridylpyridinium salt was formed. Both 1:1 and 1:2 complexes formed when iodine monochloride or iodine reacted with pyridine (80AJC1743). Formation constants for the charge-transfer complexes between iodine and pyridine (and picolines) have been measured [84JCS(P2)731], and solvent effects on the

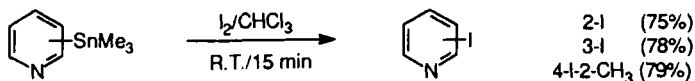
interactions between aminopyridines and iodine have been studied [86JCS(P2)1319].

Iodination is greatly assisted by activating groups in the ring, which may overcome pyridine's usual directional effects. It proved possible to control the iodination of 3-hydroxypyridine (**24**) to favor formation of either mono- or di-iodo products, with sodium carbonate proving to be a superior medium to sodium hydroxide (90S497) (Scheme 20). The specificity is rather better than in the corresponding bromination (Scheme 13). One molar proportion of iodine similarly converted 2-bromo-3-hydroxypyridine into a mixture of 6-iodo (88%) and 4,5-diiodo (8%) derivatives (90S497). Iodine monochloride converted 2,6-diaryl-1-methyl-4-thiopyridones into 3-iodo and 3,5-diiodo products (86JHC1849), whereas 2-aminopyridine was iodinated at the 5-position (92AJC877). Activating groups in the 3- or 5-positions may be necessary before successful 2-, 4-, or 6-iodination of pyridine 1-oxides can be achieved (71MI1).

Regiospecifically iodinated pyridines can be made from metallated substrates. Only very mild conditions were necessary to transform 2-, 3-, and 4-trimethylstannylpyridines into the monoiodo derivatives; the precursors, of course, had to be made from the corresponding chloro- or bromopyridines [81H(16)1161; 82CPB1731, 82H(19)168] (Scheme 21). A more direct synthesis of 2- and 4-iodopyridines made use of kinetic and thermodynamic control of pyridine lithiation. When the conditions are weakly polar, the base abstracts the proton adjacent to the annular nitrogen (cf. thiophene, furan, pyrrole, azoles). Two opposing effects, the mesomeric and inductive electron attraction by the nitrogen (which promotes 2(6)- and 4-deprotonation) and repulsion between the nitrogen electron pair and the adjacent negative charge, are influenced by the solvent. In a polar medium the latter "adjacent lone pair effect" predominates, and 4-metallation occurs (84JOC3857) (Scheme 22). Direct lithiation of 2-, 3-, and 4-aminopyridines (with the amino functions protected as pivaloyl), followed by quenching at -75°C with iodine gave 70–80% yields of the



SCHEME 20



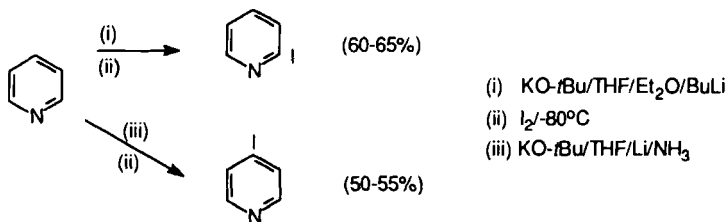
SCHEME 21

3-, 4-, and 3-iodo derivatives, respectively. When 2-fluoropyridine was treated in turn with lithium diethylamide and iodine, a 75% yield of 2-fluoro-3-iodopyridine was obtained (88JOC2740).

Pyridine, treated with iodine in the vapor phase, gave only poor yields of 3,5-di- and penta-iodopyridines (57JCS387). Decarboxylative iodination of the mercury(II) salt of nicotinic acid gave a 44% yield of 3-iodopyridine (83JOC3297).

Although there are a number of processes that introduce iodine in a nucleophilic sense, there is none analogous to that which treats pyridine with acetyl hypoiodite in an alkyl halide solvent. Unlike the chlorides and bromides, methyl iodide and diiodomethane were oxidized by the fluorine reagent (88JOC1123). Sandmeyer reactions have been frequently successful (87MI2), and halogen-exchange processes are not uncommon. When treated over an extended period with a high concentration of iodide, ion 2,6-dichloropyridine gave the diiodo analogue (80JOM147), whereas reductive dehalogenation in the presence of iodide converted 2,6-dichloronicotinic acid into 6-iodonicotinic acid (51%). Under the same conditions 3,5-dichloro-2-chloro-3-hydroxy- and 2-chloro-5-hydroxy-pyridines failed to exchange (86JOC953).

d. *Fluorination.* Pentafluoropyridine was made in an inefficient process that involved electrochemical perfluorination to give perfluoropiperidine in 8% yield, followed by treatment with iron or nickel at 600°C at low pressure [62JCS3407; 70MI1; 73MI2; 74HC(14-S2)407; 81AHC(28)1]. Perfluoropiperidine can also be made in low yield when pyridine reacts with fluorine in the presence of cobalt(III) fluoride (50JCS1966); this re-

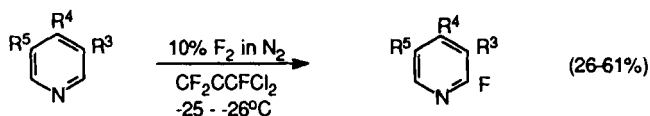


SCHEME 22

agent also transformed 4-trifluoromethylpyridine into the perfluorinated azacyclohexadiene derivative [81JCS(P1)2059].

Electrochemical fluorination of pyridine in the presence of a source of fluoride ion gave 2-fluoropyridine in 22% yield (85M11). With xenon difluoride, pyridine formed 2-fluoropyridine (35%), 3-fluoropyridine (20%), and 2,6-difluoropyridine (11%) in a reaction unlikely to be a conventional electrophilic substitution. Xenon hexafluoride has also been used (76JFC179). With cesium fluoroxysulfate at room temperature in ether or chloroform, the major product was 2-fluoropyridine (61 and 47%, respectively). Some 2-chloropyridine was also formed in chloroform solution. In methanol the entire product was 2-methoxypyridine (90TL775). Fluorine, diluted with argon in acetic acid, gave a 42% yield of the 5-fluoro derivative of 1-methyl-2-pyridone [82H(17)429].

A number of reports have detailed preparations of 2-fluoropyridines from direct reaction with molecular fluorine diluted with an inert gas and dissolved in an alkyl halide solvent (65ZC64; 87TL255; 88USP4786733; 91BCJ1081) (Scheme 23). Even when the pyridine ring is made more electron deficient, reactions such as these are kinetically competitive with annular and side-chain fluorination of benzenoid aromatics, and they may proceed through initial formation of a pyridine-fluorine complex (87TL255; 91BCJ1081). The substitution site makes an electrophilic process unlikely; initial fluorination may be at nitrogen. Certainly stable *N*-fluoropyridinium salts (**25**) are known, and they have been used as fluorinating agents (86TL3271, 86TL4465; 88JAP62/207228, 88JAP62/207230; 91BCJ1081, 91T7447). The stabilities of the salts depend on the nucleophilicities or basicities of the counteranions, and on the electronic natures and positions of ring substituents. Electron-withdrawing groups reduce the stability of **25** (91BCJ1081) (Scheme 24). The pyridine-fluorine complex is also believed to exist mainly in the ionic form (**25**; X = F) (86TL3271). Fluorinating capacities, too, depend on ring substituents; strong electron-withdrawal gives rise to a powerful source of positive

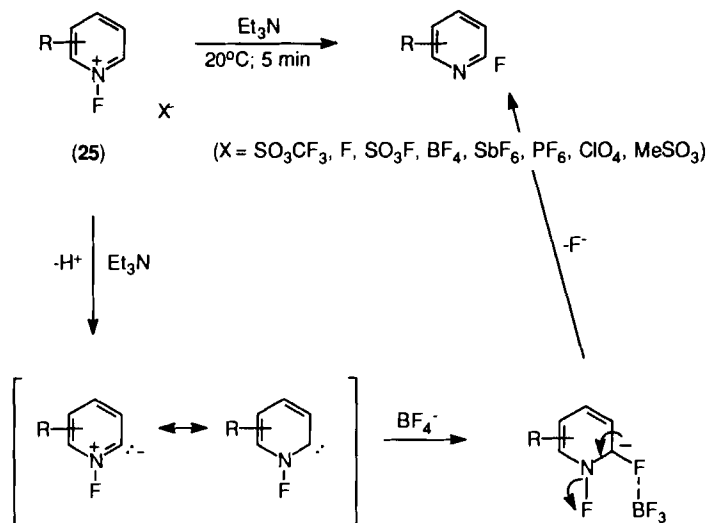


$\text{R}^3 = \text{H, Me, Cl, CO}_2\text{Me}$

$\text{R}^4 = \text{H, Me, Et, iPr, COMe, CO}_2\text{Me}$

$\text{R}^5 = \text{H, Me, Cl}$

SCHEME 23

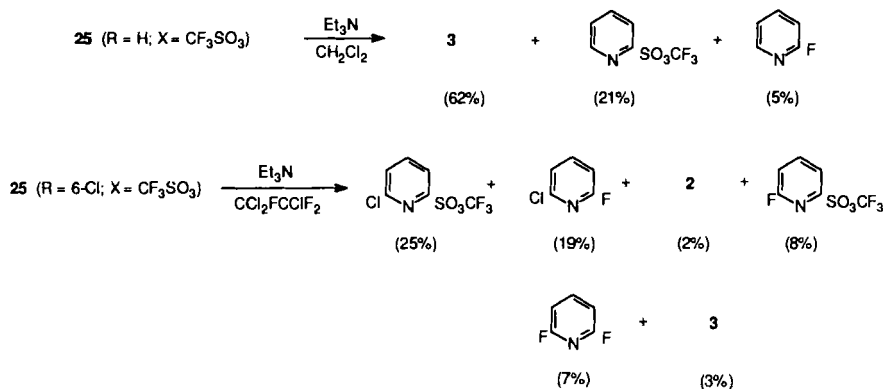


SCHEME 24

fluorine (86TL4465). Direct low-temperature fluorination of 2-trimethylsiloxypyridine gave 1-fluoro-2-pyridone, itself a fluorinating agent (83JOC761). Fluoropyridinium salts (**25**) oxidize bromide and iodide to the dihalogens (86TL3271).

Base-catalyzed decomposition of **25** (except where $\text{X} = \text{F}, \text{SO}_3\text{CF}_3$) gave high yields of 2-fluoropyridines with a wide variety of ring substituents. Because the complex (**25**; $\text{R} = \text{H}, \text{X} = \text{F}$) gave only a low yield of 2-fluoropyridine under basic conditions, a carbene mechanism was proposed, rather than one in which the salt acts as a fluorinating agent. That is, the fluoride is derived from the anion rather than from the $\text{N}-\text{F}$ bond. This is further demonstrated by the observation that the yield of 2-fluoropyridine obtained from **25** tetrafluoroborate using ammonium fluoride without any solvent was the same as when triethylamine was used. *N*-Fluoropyridinium salts are not subject to addition-elimination reactions with nucleophiles (87TL2705; 89JOC1726) (Scheme 25).

In the presence of a solvent capable of reacting with a carbene center, products other than 2-fluoropyridines were formed. Indeed, these can become the major reaction products (87TL2705; 89JOC1726), but not all products can be explained in terms of the carbene mechanism since in the 6-chloro-2-fluoropyridinium triflate (**25**; $\text{R} = 6\text{-Cl}, \text{X} = \text{SO}_3\text{CF}_3$) it is obvious that chloro is being replaced by fluoride (89JOC1726).

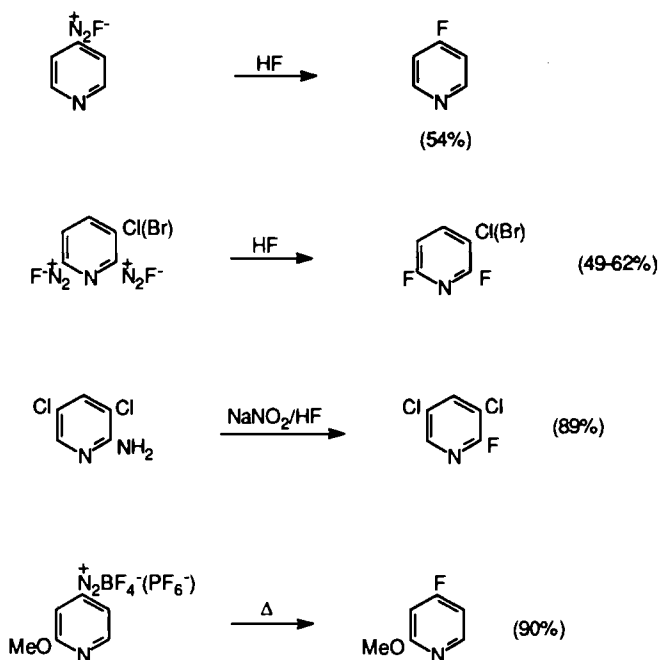


SCHEME 25

Cesium fluoroxysulfate also *N*-fluorinated pyridine (91T7447), and earlier reports that it gave 2-fluoropyridine and the 2-fluorosulfate derivative, along with "solvent-substitution" products (83CC563; 89JFC140; 90TL775) can be explained in terms of secondary transformations of the initially formed **25** [88JOC1123; 89H(28)249, 89JOC1726; 91T7447]. The cesium salt seems to be a slightly more selective reagent than elemental fluorine for such *N*-fluorinations, although yields may be no better (ca. 50%) (91T7447). The intermediacy of *N*-fluoropyridines in the synthesis of chloro- and bromo-pyridines using acetyl hypofluorite in an alkyl halide solvent has been discussed earlier (A,1,a,b).

Traditional routes to fluoropyridines have employed nucleophilic processes such as chlorine-fluorine exchange or Balz-Schiemann reactions of diazonium fluoroborates [70MI1; 73MI2]. The fluoroborates are readily converted into fluoro compounds by this method, or by ultraviolet irradiation. Typical examples have led to 2-fluoropyridines (71JA3060; 81JOC4567), and their 3- and 4-isomers [80CC1139; 81JFC(18)497, 81JOC4567; 85JHC145; 87LA857; 88JFC(38)435; 89S905; 90S681]. The 2-fluoro isomers can be prepared with great ease from the diazonium salts, even with such weak nucleophiles as fluoride ion in hydrofluoric acid (81JFC497, 81JOC4567). Scheme 26 gives some examples.

Halogen-exchange processes have been used frequently to prepare fluoropyridines. Reaction is often at elevated temperatures and has utilized a variety of fluoride sources, e.g., BrF₃, SbF₅, KF, HF (especially in dipolar aprotic solvents) [63JOC1666; 70MI1; 73MI2; 74HC(14-S2)407; 86USP4567274; 87JAP(K)62/12758]. When 2,3,5,6-tetrachloropyridine was heated at 205°C with potassium fluoride in sulfolan or dimethyl sulfoxide, a 33% yield of 3,5-dichloro-2,6-difluoropyridine was obtained; the



SCHEME 26

more reactive 2- and 6-chlorines were preferentially replaced [63JOC1666]. At higher temperatures even 3- and 5-chlorines can be displaced (64JCS3573; 88USP4782161). Between 350 and 550°C with an activated carbon catalyst, hydrogen fluoride converted 3-chloro-2-fluoro-5-trifluoromethylpyridine into the 2,3-difluoro derivative (85%) (88USP-4782161), although this may have been a radical reaction. Fluorodehydroxylation with cyanuric fluoride (60BRP845062) and fluorodenitration [72JCS(P1)2671] have also been described.

2. Rings Containing an Oxygen or Sulfur Atom

Few of these species are strictly aromatic, but reactivity with electrophiles resembles that of aromatic compounds. Much of the discussion that follows will be devoted to the pyrones and thiopyrones (the fused benz-derivatives, coumarins, chromones, flavones, and isoflavones, will be covered in Part 3).

A six-membered aromatic ring containing sulfur or oxygen must carry a positive charge. Pyriliun (**26**) is just such an example. It is unattractive to electrophiles, but nucleophiles readily attack the 2-, 4-, and 6-positions.

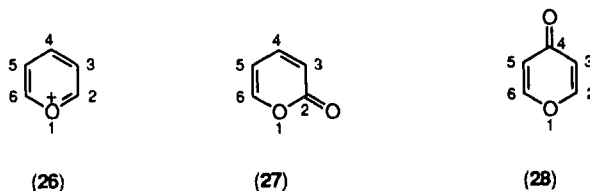
When 2,4,6-triphenylpyrilium fluoroborate (or perchlorate) was treated sequentially with sodium acetate in carbon tetrachloride and chlorine, a 3,5-dichloro salt was formed [91MIP1671661], obviously via ring-opening, chlorination of the diketone, and reclosure of the ring.

Introduction of an oxo group at the 2- or 4-positions gives 2-pyrones (**27**) and 4-pyrones (**28**) (Scheme 27). These species are readily attacked by electrophiles at the 3- and 5-positions, and also by nucleophiles, especially at the carbonyl carbon. Halogenation processes in these compounds, and in the sulfur analogues, are frequently of the addition-elimination type [83AHC(34)145; 84MI11, 84MI12; 90AHC(47)277].

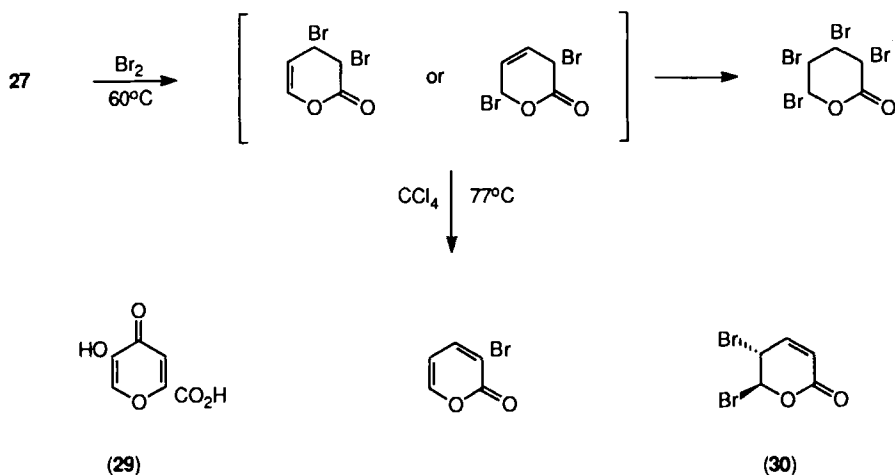
a. *Pyrans*. Since all pyran-type molecules have relatively high π -densities in the 3- and 5-positions, electrophilic halogenations will occur preferentially at these sites. Thus, bromine in carbon disulfide converted 2,4,4,6-tetraphenylpyran into the 3,5-dibromo derivative. When pyrans can be deprotonated with strong bases, the anions at the 2-, 4-, and 6-positions react readily with halogens [83AHC(34)145].

b. *Pyrones*. Both 2- and 4-pyrones also react with electrophiles at the 3- and 5-positions. The former compounds (**27**) are unsaturated lactones that display some aromaticity. Halogenations tend to occur by addition-elimination. Thus, addition of bromine to **27** at 60°C gave 3,4,5,6-tetrabromo-3,4,5,6-tetrahydro-2-pyrone. In boiling carbon tetrachloride the product was 3-bromo-2-pyrone. It has been suggested that at 60°C dibromo products form initially, and the difficulty of proton loss from a Wheland intermediate may be responsible for the reluctance of these compounds to follow the conventional electrophilic aromatic sequence. The 3-bromo-2-pyrone could be formed directly from one of the dibromides (69JOC2239) (Scheme 28). Chlorination follows much the same route.

When 6-methyl-3-phenyl-2-pyrone was treated with bromine in trifluoroacetic acid containing aluminium chloride catalyst, bromine entered the 5- and the *para*-positions giving an 80% yield of dibrominated product. When both 3- and 5-positions were occupied, as in 5-ethoxycarbonyl-6-



SCHEME 27



SCHEME 28

methyl-5-phenyl-2-pyrone, no bromination took place under these conditions. Only when 90% sulfuric acid containing silver sulfate was used as medium was it possible to *para*-brominate (and iodinate) the phenyl group (85CHE1215). Pyridinium hydrobromide perbromide converted 5-methoxycarbonyl-2-pyrone (methyl coumalate) into an 85% yield of the 3-bromo derivative [73JCS(P1)1130]. A large number of substituted 4-hydroxy- and 4-methoxy-6-methyl-2-pyrones were brominated with ease at the 3- and 5-positions. The 3-position proved to be the more reactive, requiring only bromine in dichloromethane, whereas 5-bromination required longer reaction times and the addition of iodide catalyst. The 3-acetyl derivatives reacted similarly. Under conditions favoring radical formation, NBS induced bromination of the 6-methyl group (85JHC1537).

Bromination of 4-pyrones (**28**) also takes place in the 3- and/or 5-positions with substituents modifying the orientation of attack in the usual ways. Comenic acid (**29**) gave the 6,6-dibromo derivative (84MI11). Oxime derivatives of 3-bromo-4-pyrones were converted by NBS into the 3,5-dibromo derivatives [87IJC(B)225].

When **27** was irradiated in the presence of bromine in 1,2-dichloroethane solution at -78°C , the *trans*-dibromide (**30**) was formed quantitatively (69JOC2239) (Scheme 18). Sulfuryl chloride, usually a source of chlorine radicals, gave the 3,5-dichloro derivative with 6-phenyl-2-pyrone (63JGU3361). Reaction of 6-aryl-2-pyrones with iodine monochloride in carbon tetrachloride or acetic acid gave 3-iodo products in around 70% yields. Iodine in peracetic acid gave the same products in only 50% yields

(84CHE492), and when the oxidative iodination used nitric acid as oxidizer, mixtures of 3-iodo- and 3-nitro-2-pyrones eventuated (79CHE142).

Neither pyrones nor thiopyrones have been reported to react with phosphoryl or thionyl chlorides to give chloro derivatives.

c. *Thiopyrans and Thiopyrones.* In most of their halogenation reactions these compounds resemble the oxygen analogues. Thus thiopyrones and thiopyrans are readily brominated in the 3-position [83AHC(34)145; 85S328].

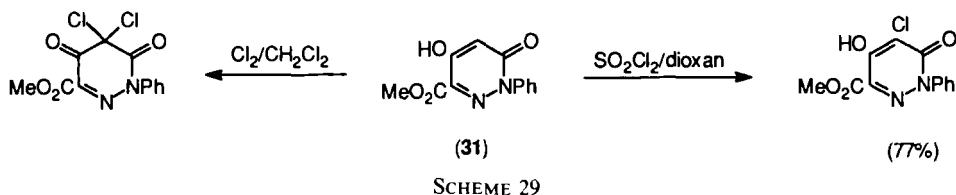
B. SIX-MEMBERED RINGS WITH TWO OR MORE NITROGEN ATOMS

1. *Pyridazines*

The halogenation of these compounds has been discussed in a number of review articles [73MI3, 73MI4; 74MI2; 79AHC(24)151, 79AHC(24)363; 84MI4; 86SC543; 88AHC(44)199; 90AHC(47)325, 90AHC(47)385].

Addition of a further annular nitrogen to pyridine decreases even further the propensity for electrophilic halogenation at all ring-carbon sites, but increases nucleophilic activity. Substituents, including *N*-oxide functions, may modify this general reactivity. Usually two or more activating substituents are needed to promote ready electrophilic attack; conjugative electron release from an *N*-oxide function assists halogenation, directing it first *para* to the oxide group, and then next to it (67CPB1411; 71MI1).

a. *Chlorination.* Although the most common method of preparation of chloropyridazines involves nucleophilic displacement of an oxo or hydroxy group, some electrophilic chlorinations are known. Reports of conversions of di- and tri-chloropyridazines into polychlorinated derivatives presumably do not refer to electrophilic chlorinations [66CI(L)904; 69USP3466283; 74MI2; 76URP388556]. Vapor phase chlorination of 3-chloropyridazine with chlorine diluted with carbon tetrachloride at 600°C gave 3,4,5,6-tetrachloropyridazine (69USP3420833). Phosphorus pentachloride at 280°C converted 3,6-dichloropyridazine into the same product [68JCS(C)2116]. Chlorination at a position vicinal to an oxo group is exemplified by the reactions of phosphorus pentachloride (alone, or in mixtures with phosphoryl chloride) or chlorine with 1,3-disubstituted pyridazine-6(1*H*)-ones to give 5-chloro derivatives. Once the aromaticity of the ring has been destroyed, as in 1,2-disubstituted pyridazin-3,6-(1*H*,2*H*)-diones, chlorine adds across the 4,5-bond. This may be followed by dehydrochlorination to give the 4-chlorinated product. Similar behavior is observed in bromination (84MI4).

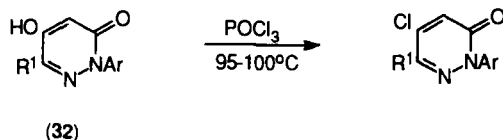


SCHEME 29

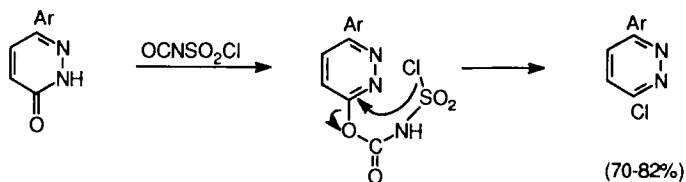
Activated pyridazines can be electrophilically chlorinated. Under a variety of conditions 2-aryl-5-hydroxypyridazin-3(2H)-ones (31) were chlorinated (and brominated) at the 4-position; with excess chlorine the 4,4'-dichloro derivative was formed (90M565) (Scheme 29). Unless there is sufficient activation, chlorination is more likely in an alkyl or aryl substituent, especially under radical conditions with reagents like NCS (80JOC1695).

As mentioned above, oxy functions at the 3-, 5-, and 6-positions are readily replaced by chlorine using phosphoryl chloride [79MI3; 80NKK33; 87CI(L)694; 89H(29)1907, 89M329; 90JHC471], chlorocarbonyl isocyanate or chlorosulfonyl isocyanate (86SC543; 87OPP80), or thionyl chloride or thionyl chloride-methane sulfonic acid [87CI(L)694]. When heated with phosphoryl chloride at 95–100°C 2-aryl-5-hydroxypyridazin-3(2H)-ones (32) gave 5-chloro derivatives (90JHC471) (Scheme 30). The 3-oxo group was not chlorinated in these compounds, which are N-substituted malonyl systems (83TL2973; 84MI20; 90JHC471), even though there are many examples in which a 3-oxo group is so displaced by chlorine [86SC543; 87CI(L)694; 89H(29)1907, 89M329; 91T8573]. At 110°C phosphoryl chloride, in the presence of a catalytic amount of pyridine, converted 6-phenylpyridazin-3(2H)-one into the 3-chloro compound in 94% yield (91T8573) (Scheme 31). Maleic hydrazide (6-hydroxypyridazin-3(2H)-one) gave a 90% yield of 3,6-dichloropyridazine when heated with nine molar equivalents of thionyl chloride and three equivalents of methanesulfonyl chloride. Although excess phosphoryl chloride gave similar results at 68–70°C, the former reagent mixture has advantages of lower boiling point and capacity for recycling [87CI(L)694].

Meisenheimer reactions of pyridazine N-oxides give deoxygenated α -chloro derivatives. If the α -position is blocked, however, γ -substitution



SCHEME 30



SCHEME 31

is observed. Thus, 3-methoxypyridazine 1-oxide gave 3-chloro-6-methoxypyridazine; 3,6-dimethylpyridazine 1-oxide gave 4-chloro-3,6-dimethylpyridazine. Nucleophilic substitutions in the *N*-oxides occur most readily at C-5 with the reactivity order being $5 > 3 > 6 > 4$. Displacements of suitably activated nitro groups have been accomplished by heating with acetyl, benzoyl, or phosphoryl chlorides (84MI4).

b. *Bromination*. Pyridazine forms molecular complexes with bromine, but direct C-substitution only occurs in the presence of suitable substituent groups. Bromine converted 1,2-disubstituted 5-bromopyridazin-3,6(1*H*,2*H*)-diones into the 4,5-dibromo derivatives (71MI1); bromine in acetic acid added to the 4,5-bond of the 1,2-disubstituted 3,6-diones (82MI1). Whereas bromine in ethanol transformed 2-aryl-5-hydroxypyridazin-3(2*H*)-ones into the 4-bromo derivatives (~85%) (90M565), 4-amino-6-chloro-3-ethoxypyridazine could be brominated at the 5-position (70CPB1680). Pyridazin-3(2*H*)-one 1-oxide and 5-hydroxypyridazine 1-oxide gave the 4,6-dibromo derivatives (75CPB923; 78CPB3884). The 1,2-dioxide of 3,6-dimethylpyridazine was resistant to bromination (73YZ59). When 3-aminopyridazine 1-oxide was brominated in acidic medium, protonation of the oxygen was apparently followed by nucleophilic bromination and elimination of water to give 3-amino-6-bromopyridazine (83JOC1064).

c. *Iodination*. Complexes of iodine and pyridazine are stable even above 200°C (70CC188). As with other halogenations, electrophilic iodination needs strong activation from ring substituents. Iodine in aqueous sodium carbonate gave the 4-iodo derivative of 5-amino (and 5-hydroxy)-2-arylpyridazin-3(2*H*)-one-6-carboxylic acids (90JHC471). However, 3-chloro-6-(2'-methoxybenzyl)pyridazine iodinated in the substituent, *para* to the methoxy group (87SC1907). The potential of metallic derivatives is evident from the synthesis of 3,6-dichloro-4-iodopyridazine in 32% yield from the lithium derivative of 3,6-dichloropyridazine (90JHC1259).

In a nucleophilic substitution procedure a number of chloropyridazines were converted by sodium iodide into the iodo analogues (77AJC2319).

d. *Fluorination*. Electrochemical fluorination of 4,5-dichloropyridazin-3(2*H*)-one formed the 6-fluoro derivative [89JAP(K)01/29366]. Fluoropyridazines are most conveniently made by halogen-halogen exchange. The 5-chloro group in some 1-aryl-4,5-dichloropyridazin-6(1*H*)-ones proved the most labile when treated with potassium fluoride (88M11), whereas selective fluorination of 3,4,5,6-tetrachloropyridazine occurred most readily at positions adjacent to the annular nitrogens, although all four chlorines were ultimately replaced (83JFC301) (Scheme 32). When further treated with cobalt(III), fluoride perfluoropyridazines lose nitrogen to form polyfluorinated alkenes [81JCS(P1)2059]. Although 3-fluoro-6-methylpyridazine could be prepared from the 3-diazonium fluoroborate, it proved to be unstable (77AJC2319).

2. Pyrimidines

The biological importance of the pyrimidine nucleus has attracted much attention to the synthesis and manipulation of halogenated derivatives. Aspects of pyrimidine halogenation have been surveyed in a number of review articles and monographs [80UK1260; 81H(15)583, 81UK1559; 84M15; 85AHC(38)229; 88AHC(44)199; 90AHC(47)325].

Electrophilic halogenation generally occurs only with difficulty in the absence of activating groups, with the 5-position being the most readily substituted [84ACS(B)341, 84JHC385, 84S252; 85JMC1864]. A number of pyrimidine-halogen adducts are known, and reactions that occur at low temperatures may proceed in the same manner as pyridine with N-preceding C-halogenation. There has been much more emphasis placed on synthesis of fluoropyrimidines than with most other heteroaromatic compounds.

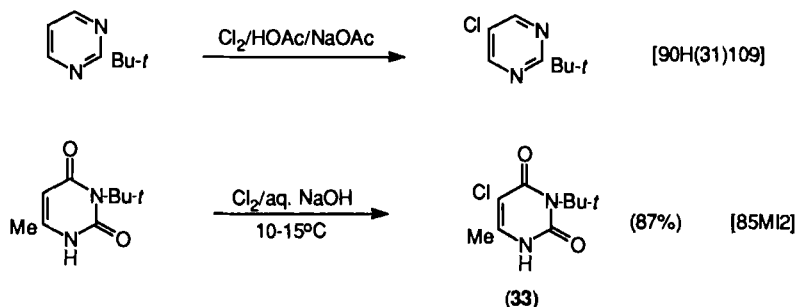
a. *Chlorination*. Activated pyrimidines have been 5-chlorinated by a variety of chlorine sources: chlorine dissolved in a suitable solvent (81S701; 89CZP263369), chlorine in the presence of base (e.g., acetate



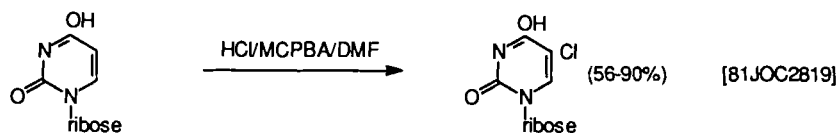
SCHEME 32

buffer) [85ZPK1185; 90H(31)109], phenyl iododichloride (82CJC554), NCS (66T2401; 83JOC2719; 84TL3325; 92AJC877), sulfonyl chloride with ferric chloride catalyst (83JHC219), chloride with an oxidizing agent (81JOC2819), and enzymic methods (84MI18; 87CL2311). Although most of the reported reactions are for pyrimidines activated by "hydroxy" or amino functions in one or more of the 2-, 4-, and 6-positions, a 2-*t*-butyl group proved sufficiently activating to permit 5-chlorination in good yield [90H(31)109] (Scheme 33). 5-Chloropyrimidine has not been made by direct methods, and the 2- and 4-methyl derivatives are mainly chlorinated laterally by NCS (74AJC2251). A high yield of the 5-chlorouracil (**33**) was obtained when 3-*t*-butyl-6-methyluracil was chlorinated in aqueous alkali (85ZPK1185). Oxidative halogenations have included the preparation of 5-chloropyrimidine nucleosides using HCl and *m*-chloroperbenzoic acid in a dipolar aprotic solvent (81JOC2819), and the synthesis of 5-chloro-uracil and -cytosine (but not -thymine) with potassium chloride and hydrogen peroxide in the presence of chloroperoxidase (87CL2311) (Scheme 34). Barbituric acid and its 1,3-dimethyl derivative were similarly transformed into the 5,5-dichloro derivatives (84MI18).

The introduction of more than one chlorine by electrophilic methods is seldom possible, although 2,4,5-tri- and 2,4,5,6-tetra-chloropyrimidine are commercially available (both are lachrymators and vesicants) (74MI2). Synthesis of such compounds may require ring synthetic methods and nucleophilic processes since only C-5 is at all prone to electrophilic chlorination, but 5-chloro-2-phenylpyrimidine has to be made by the reaction of chloromalondialdehyde with benzamidine (51JCS2323). "Metallic" derivatives frequently provide substrates for electrophilic chlorination. Chlorodemercuration (using sulfur monochloride) gave a 65% yield of 5-chlorouracil (85CHE322; 88BAP499), whereas displacement of a 6-trimethylsilyl group by chlorine (using NCS) has been reported (84TL3325).



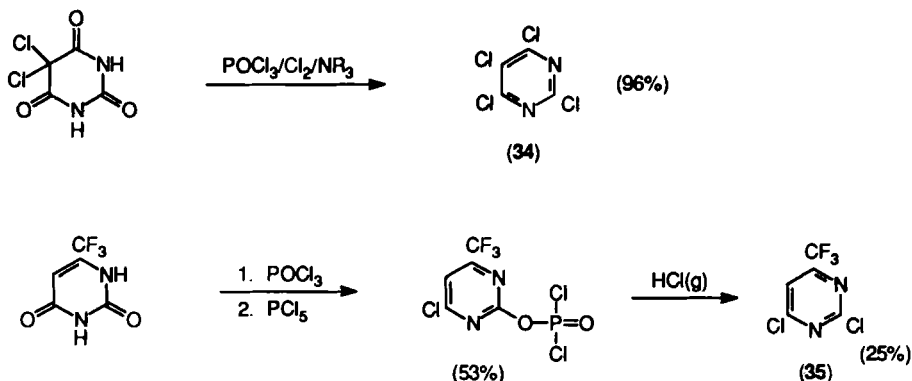
SCHEME 33



SCHEME 34

An isolated *N*-oxide function on pyrimidine is seldom sufficiently activating to allow C-halogenation [84H(22)1195].

The most common nucleophilic process for pyrimidine chlorination is the conversion of oxy or hydroxy compounds using hot phosphoryl chloride and related reagents. This route is especially applicable to the synthesis of 2-, 4-, and 6-chloropyrimidines [81S701; 82CPB2410; 83JHC219, 83JHC311; 84GEP3228712, 84MI21, 84S252; 85ACS(B)691; 86ACS(B)764, 86JHC1079, 86TL6377; 87CHE554; 88M953; 89CHE530; 91MI1]. Reactions are frequently carried out in the presence of a tertiary amine base [74MI2; 82CPB1947; 84GEP3228712, 84H(22)79, 84JHC1161; 87JHC205, 87JHC1243], as in the preparation of 2,4,5,6-tetrachloropyrimidine (34) (84GEP3228712) (Scheme 35). When 1-methyl-5-phenyl-2(1*H*)-pyrimidinone was heated with phosphoryl chloride, a low yield of 2-chloro-5-phenylpyrimidine was obtained. Such dealkylation accompanying chlori-

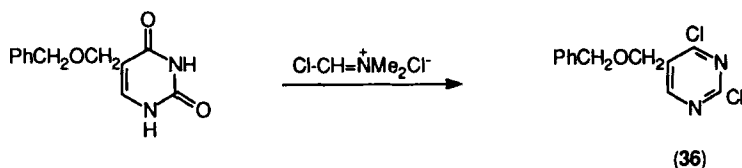


SCHEME 35

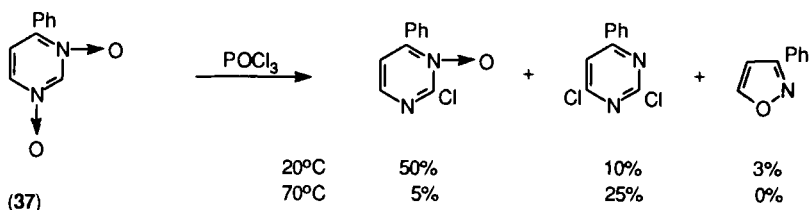
nation is not restricted to the pyrimidinones (it was noted earlier with 6-methyl-1,6-naphthyridin-5(6*H*)-one) (80JHC1479; 87CHE554). Reaction of 6-trifluoromethyluracil in turn with phosphoryl chloride, phosphorus pentachloride, and gaseous HCl gave a 25% yield of 2,4-dichloro-6-trifluoromethylpyrimidine (**35**). The hydrogen chloride is necessary to hydrolyze the intermediate 2-dichlorophosphate ester (Scheme 35). A similar reaction sequence was followed when 5-chloro-6-trifluoromethyluracil was converted into 2,4,5-trichloro-6-trifluoromethylpyrimidine (83JHC219). In a related reaction pyrimidin-2(1*H*)-thione formed 2-chloropyrimidine when treated with elemental chlorine or sulfuryl chloride below room temperature in an acetic acid-dichloromethane medium (81USP4256888). When highly acidic conditions and elevated temperatures are contraindicated, chloromethylenedimethylammonium chloride (made *in situ* from dimethylformamide and phosgene or thionyl chloride) is an effective reagent at room temperature, and it has been used to convert 5-benzyloxymethyluracil into its dichloro derivative (**36**) (66CCC1053) (Scheme 36). This reagent has mainly been applied in nucleoside transformations.

When treated with phosphoryl chloride at room temperature, 4-phenylpyrimidine 1,3-dioxide (**37**) was chlorinated with the loss of one or two oxide functions. The reaction products were a function of temperature (see Scheme 37), and when there was a methyl group in the 5-position the ratio 2-chloro 3- : 2-chloro 1-oxide became 3.5 : 1. If all of the positions α and γ to the *N*-oxide functions were blocked, the usual Meisenheimer process did not occur; instead lateral chlorination of the adjacent methyl groups was observed (81CHE383; 83CPB4533). No 2- and 4-chloropyrimidines were formed on similar treatment of 2- and 6-methylpyrimidine 1-oxides; deoxygenation and lateral chlorination only were noted [83H(20)991].

Conversion of diazonium halides into chloropyrimidines has employed excess chloride ion or copper(I) chloride. These reactions have been mainly used to make 2- and 4-chloropyrimidines although the 5-chloro derivatives are also available in this way. One drawback is the substantial amount of oxo product formed, especially when 2-aminopyrimidines are



SCHEME 36



SCHEME 37

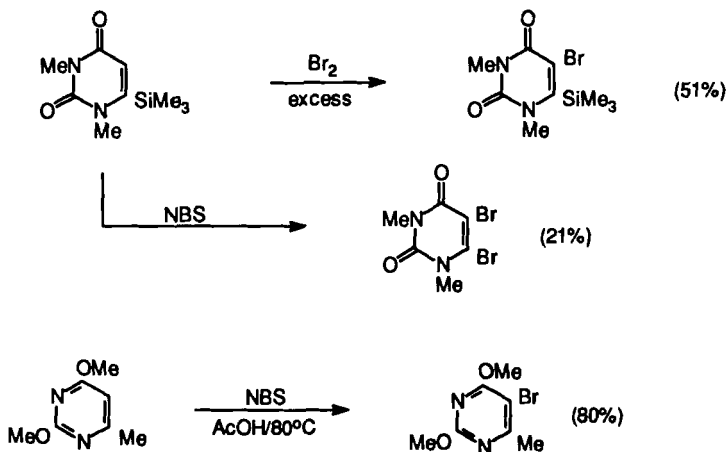
used as substrates [66MI1; 67JCS(C)1204, 67JCS(C)1928; 83CHE91]. The method also works with aminopyrimidine 1-oxides as long as the medium is not so acidic that electrophilic 5-chlorination can occur (83CHE91).

Although transhalogenations have not found major application to the preparation of chloropyrimidines, the conversion of 5-bromo-6-hydroxypyrimidin-4(3*H*)-one into the 5-chloro derivative by warming with HCl in dimethylformamide provides the best route to that derivative (64JGU3908).

b. *Bromination.* The volume of publication devoted to pyrimidine bromination is daunting, with both synthetic and mechanistic considerations receiving attention. The heterocycles can be converted into 5-bromo derivatives with bromine in solvents such as benzene or nitrobenzene. Yields for 5-bromopyrimidine itself lie in the range 71–88%, but the reaction is preceded by a vigorous reaction at lower temperatures when (presumably) *N*-bromo compounds and perbromides form. The procedures involved are probably not conventional electrophilic aromatic substitutions [57CB1837; 58AG571; 73JHC153; 90AHC(47)325]. Vapor phase bromination at 230°C also gave a 62% yield of 5-bromopyrimidine (73JHC153).

Activating substituents greatly assist the reactions that have used elemental bromine in a variety of solvents [80CPB3576; 81RTC267, 81S701; 83JOC2719; 84H(22)2739, 84TL3325; 85CHE1399; 86S555; 88CPB3887; 91JHC1901], often in the presence of base [82JAP(K)40497; 85ZPK1185; 90H(31)109], NBS [66T2401; 74AJC2251; 83CHE91, 83JOC2719; 84JHC969, 84TL3325; 86S555], a bromide under oxidative conditions (81JOC2819; 87CL2311), and enzymatic methods (89MI1). Displacement of a trimethylsilyl or mercury group has also been successful (84TL3325; 88BAP499) (Scheme 38).

The degree of activation is important, as is the nature of the substituent. A methyl group in the 4-position is brominated on the exocyclic carbon in basic medium unless there is an amino group at C-2 (60CB2405; 74AJC2251), whereas a 4-methyl group is less activating than a 2-methyl



SCHEME 38

substituent. Bromination of 2-methylpyrimidine gave 5-bromo-2-tribromomethylpyrimidine [54CI(L)1203; 60AC(R)351]. 4-Phenylpyrimidines are readily 5-brominated (73JHC153, 73JHC409; 78CHE1132).

Amino, hydroxy, or oxo groups in the pyrimidine ring greatly assist electrophilic bromination, and the relevance of such substrates as uracil, barbituric acid, and related compounds to biological systems has stimulated studies of their bromination. When a potentially tautomerizable amino or hydroxy group is situated α or γ to a ring nitrogen, 5-bromination occurs with great facility even in aqueous solution [67JCS(C)1922; 71BAU2108; 81S701; 83JOC1064; 91JHC1901]. If the 5-position is blocked, as in 5-phenyl- and 4,5-dihydroxypyrimidines [64JCS1001; 77JCS(P1)1862], bromination may fail, but a 5-hydroxy group is phenolic enough to activate the adjacent carbon sites.

Barbituric acid reacted with bromine to give in turn the 5-bromo and 5,5-dibromo derivatives. Subjection of the latter to base-induced dehydrobromination or reduction converted it back into the monobromo species. *N*-Alkylbarbituric acids behaved similarly [62HC(16)172; 74JCS(P1)2095]. Uracil was brominated in aqueous solution initially in much the same way. A 5-bromo derivative was formed at first, and then (38), apparently a consequence of addition of hypobromous acid. Although quite stable, (38) can be converted back into the monobromo derivative when boiled with mineral acid. 1,3-Dimethyluracil, substituted at C-6 by chlorine, bromine, or iodine, was both mono- and di-brominated at C-5 by bromine (81S701). Cytosine and related compounds behaved similarly [59JOC11; 90AHC(47)325].

Although 2-, 4-, and 5-methoxypyrimidine 1-oxides could not be brominated unless forcing conditions were used, strongly electron-donating groups such as amino at C-2 and C-4 greatly assist 5-bromination (78CHE1132; 83CHE91, 83JOC1064). 2-Amino-4-phenylpyrimidine 1-oxide was converted quite readily by NBS into the 5-bromo derivative (83CHE91). Deoxygenative bromination of activated pyrimidine *N*-oxides can take place concurrently with direct bromination [84H(22)1195].

The mechanisms of bromination of the 2-oxo (78CJC2970; 80JOC2072; 81JOC4172) and 4-oxo derivatives of pyrimidine (79JOC3256; 81JOC4172) and their *N*-methyl derivatives have been studied in detail (Scheme 39). For pyrimidin-2(1*H*)-one (**39**; R = H), the kinetic data support a rate-determining attack at high acidity (pH < 2) by bromine upon a covalent hydrate (**41**; R = H), which, as an enamine, is rapidly brominated in the 5-position to give **42** (R = H), which is capable of further hydration to form **43** (R = H). Slow acid-catalyzed conversion of **42** or **43** into 5-bromopyrimidin-2-(1*H*)-one (**44**; R = H) follows. Obviously, the reaction is complex, and when excess bromine is present dibromo products (**45**; R = H) can form (77JOC3670; 78CJC2970) (Scheme 39). *N*-Methyl groups assist the process (74CJC451). At lower acidities (pH > 4) the formation of the pseudo base appears to be rate-limiting because at high acidity values the reversal of **41** to the cation (**40**) is fast in comparison with the rate of bromine attack, whereas at low acidities the reverse is true. Results obtained in the pH range 2–4 are consistent with a slow changeover in mechanism (80JOC2072).

A separate kinetic study of pseudo-base formation and decomposition yielded rate coefficients in good agreement with those obtained from the bromination studies (77JOC3670; 78CJC2970; 80JOC2072). Covalent hydrate formation is also implicated in the bromination of 5-bromopyrimidin-2(1*H*)-one. Rates measured in aqueous solution in the pH range 0–6 indicated a change in reaction order around pH 2.5 consistent with the substrate reacting as its covalent hydrate (**46**; R=H) present to the extent of about 5% (86CJC1267) (Scheme 39).

A parallel study of aqueous bromination of pyrimidin-4(3*H*)-one and its *N*-methyl derivatives also pointed to an addition–elimination process involving cationic intermediates. The kinetic results for these substrates differed from those of **39** (in which the pseudo bases dehydrate as neutral molecules) in that the intermediates dehydrated in cationic forms (79JOC3256). Again, the covalent hydrates, though present to only a minor extent (~0.0003%), were the reactive species in the bromination process. Pyrimidin-4(3*H*)-one, as its covalent hydrate, reacts 600 times faster than it does itself; the rate enhancement is even greater ($\geq 10^4$) for the 2-isomer, which exhibits a higher degree (~0.05%) of covalent hydration.

of both addition and substitution can be identified in aqueous solution, and 5,5-dibromo products are common. Uracil bromination parallels that of pyrimidin-2(1*H*)-one in that addition products, including covalent hydrates, form rapidly. Acid-catalyzed dehydration to 5-bromouracils is a much slower subsequent step. The kinetic results demonstrate that substrates with at least one NH group react predominantly as anions at higher pH values (79CJC626; 80JOC830; 81RTC267). Analogous kinetic studies for cytosine and its N-substituted derivatives in the pH range 0–5 showed that adducts form from attack of bromine on the free base, followed by capture of the cation produced by water (82JOC1018).

Occasional reports of radical bromination of pyrimidines have appeared. Reactions in which an alkyl substituent is brominated probably involve radicals, but there are examples of annular bromination too. Reaction of 1,3-dimethyluracil with NBS in carbon tetrachloride in the presence of benzoyl peroxide gave a >95% yield of the 5-bromo derivative (85SC1001; 91JHC1901). When the 5-position is blocked, α -halogenation of an alkyl substituent takes place [80H(14)1953]. Both 4,5-di- and 4,5,6-tri-methylpyrimidines were brominated at the 5-methyl group by NBS in carbon tetrachloride, and at the 4-methyl group by bromine in acetic acid, providing a highly regioselective side-chain bromination process (91JOC5610).

As with the preparation of chloropyrimidines, "hydroxy" pyrimidines can be converted into the bromo derivatives by heating with phosphoryl bromide, or diazonium salt transformations can be used [64JOC943; 66MI1; 67JCS(C)1204]. Transhalogenations are also possible. The high price of phosphoryl bromide makes this last approach potentially important since treatment of 2-chloro- and 2-chloro-4,6-dimethyl-pyrimidines with the relatively inexpensive phosphorus pentabromide gave more than 50% of the bromo analogues [67JCS(C)1204].

c. *Iodination.* Complex formation between iodine and pyrimidine has been reported (91RC1024). Although 5-iodopyrimidine is known, it cannot be made by direct iodination of pyrimidine. One or more electron releasing groups is necessary before reaction is successful with NIS as the reagent of choice (66T2401). Direct iodination of suitably activated pyrimidines has used NIS in acetic acid (83JOC2719; 86S555), in ethanol or ethanol-chloroform mixtures (81RTC267), and in a mixture of trifluoroacetic acid and its anhydride (88SC855). *In situ* generation of NIS using sodium iodide with NCS has been recommended (84TL233). Iodine in pyridine, pyridine–acetic acid, pyridine–dimethylformamide [82JAP(K)40497; 83JOC2719]; in aqueous ammonia (83CHE1008); or in ethanol with silver sulfate (90SC3391) have also proved useful. Generation of the electrophilic iodine by the action of an oxidizing agent on sodium iodide has also been

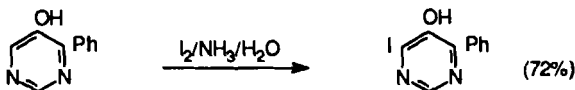
reported (81RTC267; 90JOC4928). Iodine monochloride has been used occasionally [82CJC554; 83ACS(B)345; 84S252]. It can be generated *in situ* by passing chlorine gas through a solution of iodine in dioxan (84S252).

The 2- and 4-aminopyrimidines were readily iodinated in greater than 50% yields, as is pyrimidin-4(3*H*)-one (but not the 2-isomer) (84S252). Even in 5-hydroxypyrimidine there was sufficient activation for the 6-iodo derivative to be formed. Unexpectedly, 5-hydroxy-4-phenylpyrimidine 1-oxide failed to react with iodine in aqueous ammonia, presumably for steric reasons (83CHE1008, 83CHE1012) (Scheme 40). With NIS in trifluoroacetic acid–trifluoroacetic anhydride medium 2,4-dimethoxypyrimidine (and related uracils) were 5-iodinated; iodine monochloride, however, induced cleavage of the ether groups with formation only of 5-iodouracil (88SC855). Iodine, or an iodide with ceric ammonium nitrate, converted protected uracil nucleosides into their 5-iodo derivatives in >90% yields (88TL2855; 90JOC4928). Similar high yields were obtained when 1-alkyluracils were treated with iodine monochloride in methylene chloride (82CJC554) or in the presence of triethylamine [85ACS(B)501]. Radio-iodinated 5-iodo-2-thiouracil was made directly in a two-phase reaction at pH 7 with Iodo-Gen (89MI2). Cross-linked polystyrene-4-vinylpyridinium dichloroiodate proved an effective iodinating agent for uracils (>90% yields) [89JCS(P1)2279]. Heating pyrimidin-2(1*H*)-one hydrochloride in a phosphate buffer at pH 1–3 with sodium dichloroiodide gave a 75% yield of 5-iodopyrimidin-2(1*H*)-one [85ACS(B)691].

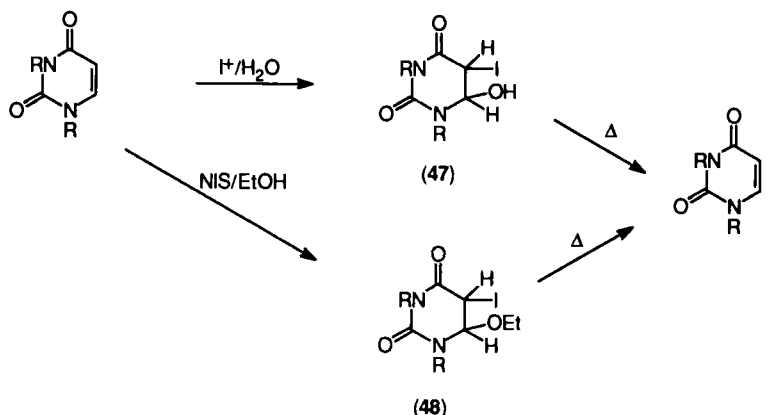
It has been demonstrated that when uracils are iodinated with electrophilic iodine (using chloroamine-T and iodide or Iodo-Gen) in aqueous solution, or NIS in ethanol or chloroform–ethanol, addition products (**47** or **48**) form initially, eliminating water or ethanol when heated (81RTC267) (Scheme 41).

Metallated pyrimidines are useful substrates for preparing iodopyrimidines. Halodemercuration is known (85CHE322; 88BAP499), but generation of suitable anions with lithiating agents has become much more common (83CPB2164; 91JHC283). The 5-lithio derivative of 4-chloro-2,6-dimethylpyrimidine reacted with iodine in tetrahydrofuran to give the 5-iodo derivative in 86% yield (91JHC283).

Trans-halogenation processes are especially important for the preparation of iodo (except 5-iodo) pyrimidines. Chloro- and bromo-pyrimidines



SCHEME 40



SCHEME 41

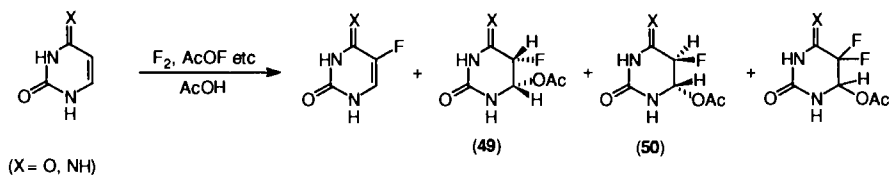
readily formed the iodo analogues when treated with sodium iodide and HI in acetone. 4,6-Dichloropyrimidine gave the 4,6-diiodo product in this way [62JMC1335], but only extranuclear iodination took place when 2,4-dichloro-5-chloromethylpyrimidine was exposed to these reagents [66LA(692)119]. Treatment of 2-chloro- or 2-bromo-pyrimidine with hydriodic acid at 0–5°C gave moderate yields of 2-iodopyrimidine [73AJC443]. Chlorines in the 4- and 6-positions appear to be more labile than those at C-2. Sodium iodide converted 2,4,6-trichloro-5-trifluoromethylpyrimidine into the 4-iodo and 2,4-diiodo derivatives [86JHC1079]. Polyfluorinated pyrimidines reacted with sodium iodide in dimethylformamide to displace fluorine atoms in the 4- and 6-positions [69JCS(C)1866; 73MI2].

Conversions of diazonium salts into iodopyrimidines have been reported [66MI1; 67JCS(C)1204].

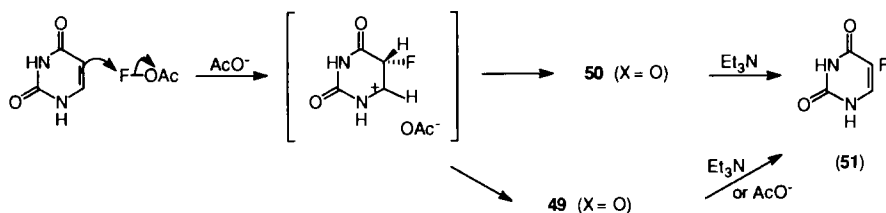
d. *Fluorination.* Provided that the ring is sufficiently activated, direct 5-fluorination is possible. Fluorine in acetic acid or anhydrous HF gave 5-fluoropyrimidin-2(1*H*)-ones [77CCC2694], and 5,5-difluorination of 6-*O*-cyclouracil nucleosides occurred under similar conditions [83TL1055]. 5-Fluoro-uracil and -cytosine were prepared analogously [80TL4605; 81CB1176; 82CPB887, 82JAP(K)57/154171; 88EUP257361]. Barbituric acid, too, formed a 5,5-difluoro derivative, but the monofluoro species is not yet known [74JCS(P1)2095]. Uracil gave 5-fluorouracil when fluorine was passed into an aqueous suspension of the azine at room temperature [81CPB3181; 82CPB887; 84TL4885]. Higher yields were achieved with perfluoromethanol as fluorinating agent, with the graphite intercalate, C₁₉XeF₆ [80TL277], or with fluorine in H₂SiF₂ [84JAP(K)59/16680]. Other

successful reagents have included acetyl hypofluorite [85JOC4152; 86CJC424, 86JOC1466; 88ACR307, 88JCS(P1)1203, 88JCS(P1)2547], trifluoroacetyl hypofluorite (81CPB3181), cesium fluoroxysulfate (83CC563; 90T3093), fluorine monoxide (81CB1176), and *N*-fluoropyridinium salts (90JA8563). Small-scale preparations involving direct fluorination of uracil with fluorine or trifluoroacetyl hypofluorite gave yields in the region 76–92%, but scaling-up considerably reduced the efficiency (81CPB3181). Problems arising from difluorination of highly activated substrates have been overcome by incorporating an electron-withdrawing group in the ring. Direct fluorination of uracil-5-carboxylic esters, amides, or nitriles in the presence of water, methanol, or acetic acid, followed by mild hydrolysis of the products gave up to 92% yields of 5-fluorouracil (81CPB3181). Mild fluorination of uracil derivatives with cesium fluoroxysulfate in alcoholic solvents gave 54–79% yields of 5-fluoro products that formed via an initial addition process. Elimination of alcohol in the presence of triethylamine completed the reaction (90T3093). It is not possible to prepare 5-fluoropyrimidine by direct fluorination; a ring-synthetic process from ethyl fluoroformylacetate with *S*-methylurea was, however, successful (65MI2).

All of the direct fluorinations reported appear to be addition–elimination processes with solvent involvement (Scheme 42). A study of the mechanism and stereochemistry of uracil and cytosine fluorination using fluorine and acetyl hypofluorite has implicated a radical-cation mechanism (86JOC1466). The effect of acetate ion on the products proved to be important. In its absence both *cis*-isomers (**49**) and *trans*-isomers (**50**) were observed in the reaction mixture, but only **50** [and 5-fluorouracil (**51**)] in its presence. The process has been rationalized in terms of the reaction diagram shown in Scheme 43. NMR studies have revealed that the acetate from the solution containing acetate ion, rather than the residue from acetyl hypofluorite, binds to the 6-position of uracil to form the intermediates (**49** and **50**). Acetate is a sufficiently strong base to induce *trans*-elimination of acetic acid from the *cis*-isomer (**49**). 5-Fluorouracil (**51**) was obtained in 45% yield from these reaction sequences (86CJC424).



SCHEME 42



In the 1-substituted uracils, the substituent exerted a profound effect on the stabilities of the reaction intermediates, but the intermediate adducts in the cytosines rapidly deaminated in water to yield uracil analogues [88JCS(P1)1203].

Reaction of 1,3-dimethyluracil with cesium fluoroxyacetate in methanol at room temperature initially produced a mixture of *cis*- and *trans*-isomers of 5-fluoro-6-methoxy-1,3-dimethyl-5,6-dihydrouracil (analogous to **49** and **50**) in an 11.5:1 ratio. Base-induced elimination of methanol gave 5-fluoro-1,3-dimethyluracil (89%) (83CC563). Fluorination of 5-substituted barbiturates with perchloryl fluoride was shown to be first order in each component; electron-donating groups accelerated the reaction, and rate coefficients correlated well with σ_p as in other aromatic halogenations (79JOU357). The exocyclic nitrogen of 2- and 4-aminopyrimidines has been fluorinated (84JFC355).

Halogen exchange reactions, too, are valuable sources of fluorinated pyrimidines, especially 2-, 4-, and 6-fluoro derivatives. Sources of fluoride ion have included hydrogen, sodium, potassium, cesium, antimony, silver fluorides, and sulfur tetrafluoride. All of the reactions required heating. Prepared from nucleophilic fluorination processes have been 2,4,6-trifluoro- (70%) (62JOC2580), (93%) (85EGP221736), (90%) (66USP3280124); 2-fluoro- (72CHE1281), 2,4- (83GEP3131735), and 4,6-difluoro- (~70%) (60JA5107); 2,4-difluoro-6-methyl- (~60%) (67YZ1315); 4-fluoro-2-methoxy- (73MI1), 2,4-difluoro-6-trifluoromethyl- (73%) (90EUP445644); and 2,4-difluoro-5-trifluoromethylpyrimidines (86JHC1079). The last named product was prepared by heating the chloro analogue with a mixture of potassium and antimony fluorides.

Contact time very much controls the degree of conversion of polychlorinated pyrimidines heated in sealed tubes with solid potassium fluoride [81JFC(17)385], and selectivity can also be achieved by careful control of reaction conditions and reagents. With 2,4,5-trichloropyrimidines, substituted at C-6 by chloro, methyl, chloromethyl, di- or tri-chloromethyl, sodium or potassium fluoride use only resulted in nuclear fluorination.

Hydrogen fluoride can displace chlorines on either side chain or nucleus (especially 2-chloro), and antimony fluoride is specific for all chlorinated methyl groups. Sodium fluoride initially replaces a 4-chloro group (82JFC495). Some of these processes have been subjected to kinetic investigation, which demonstrated that in polar, aprotic solvents fluorine–chlorine exchange is a pseudo first-order, consecutive reaction (87JFC373).

When heated with potassium fluoride in ethylene glycol 2,6-dimethoxy-4-trimethylammoniopyrimidine salts were converted into the 4-fluoro derivatives in good yield (61JOC3392). Similarly prepared were 4-fluoro-2-isopropyl- (81%) (78AJC1391) and 2-fluoro-4-phenyl-pyrimidine (74RTC111). Anhydrous potassium fluoride in tetraglyme with a catalytic amount of dicyclohexano-18-crown-6 at 150–160°C converted uracil into 2,4-difluoropyrimidine. This process solved the problem of having to use an autoclave or dimethylformamide as solvent, because in tetraglyme (bp 275–276°C) the more volatile fluoro products could be distilled directly from the reaction mixture uncontaminated by solvent. With this procedure, high yields of 2,4-difluoro- (82%), 2,4-difluoro-5-methyl- (85%), 2-amino-4-fluoro- (66%), and 4-amino-2-fluoro-pyrimidine (16%) were obtained. Under similar conditions 2-chloro-5-methoxypyrimidine was converted into the 2-fluoro analogue (85JHC149).

Synthesis of fluoropyrimidines from diazonium salts does not always give good yields [74JCS(P2)204]; about 10% yields of the 2-fluoro-4- and 4-fluoro-2-methoxypyrimidines were made by this method (85JHC149).

3. *Pyrazines*

Aspects of pyrazine halogenation have been discussed in a number of articles [72AHC(14)99; 74MI2; 82HC(41)1; 84MI6; 88AHC(44)199; 90AHC(47)325]. The compounds have reduced reactivity toward electrophiles, especially when the conjugate acid of pyrazine can form under the chosen reaction conditions. Halogenation can, nevertheless, take place if suitable activating groups are present. Nucleophilic reactions are much more facile. Much of the recent work on pyrazine halogenation has been devoted to studies of the *N*-oxides.

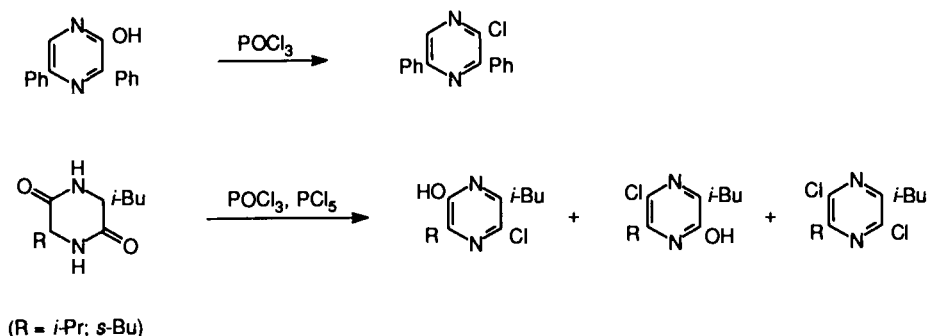
The suggestion has been made that examples of pyrazine and alkylpyrazine halogenation that are heterolytic rather than homolytic take place by an addition–elimination pathway [66CI(L)1721; 72AHC(14)99; 90AHC(47)325]. It is also likely that *N*-halogenated species are formed initially in reactions that lead ultimately to C-halogenated pyrazines (61JOC2360). The increasing availability of lithiated pyrazines will offer another potential route to halogenated derivatives (91JOM301).

a. *Chlorination.* Selectivity is possible by careful reagent choice for the chlorination of alkylpyrazines. Exclusive 3-chlorination ($\sim 30\%$) of 2-alkyl derivatives was accomplished by using thionyl chloride in dimethylformamide at 20°C ; the 5-chloro isomers predominated when pyrazines with bulky groups at C-2 reacted with a mixture of phosphoryl chloride and phosphorus pentachloride [72JCS(P1)2004]. In the first case the dimethylformamide appeared to play a crucial role because little chlorination was observed in its absence.

Pyrazine has been chlorinated at 400°C in the vapor phase to give 2-chloropyrazine, or at lower temperatures under catalytic conditions. Higher temperatures and excess chlorine or phosphorus pentachloride gave rise to high yields of tetrachloropyrazine [72AHC(14)99; 74MI2].

Reaction of methyl 2-aminopyrazine-3-carboxylate with chlorine in acetic acid gave the 5-chloro derivative along with product in which the amino group had been chlorinated. Bisulfite readily reduced the *N*-chloro group (79MI1). Both 3,6- and 5,6-dialkylpyrazin-2(1*H*)-ones were halogenated with NCS (or NBS or NIS) at room temperature in dimethylformamide at the 5- and 3-positions, respectively [91H(32)2407]. 2-Aminopyrazine was converted by NCS in refluxing chloroform into 2-amino-5-chloropyrazine in low yield (92AJC877).

It is usually much more convenient to prepare chloropyrazines by nucleophilic substitution processes. These reactions may not follow simple addition-elimination courses, and it may be necessary to invoke an ANRORC mechanism in some cases (71RTC207; 72RTC949). Chlorinated pyrazines have been traditionally made from pyrazinones or *N*-oxides (see below) treated with the usual reagents. Phosphorus pentachloride can lead to mixtures of products, and polyhalogenation has been observed at elevated temperatures. Some examples are shown in Scheme 44 [66CI(L)1721; 82JHC407, 82JHC1061, 82MI2; 83CPB20, 83JHC311].



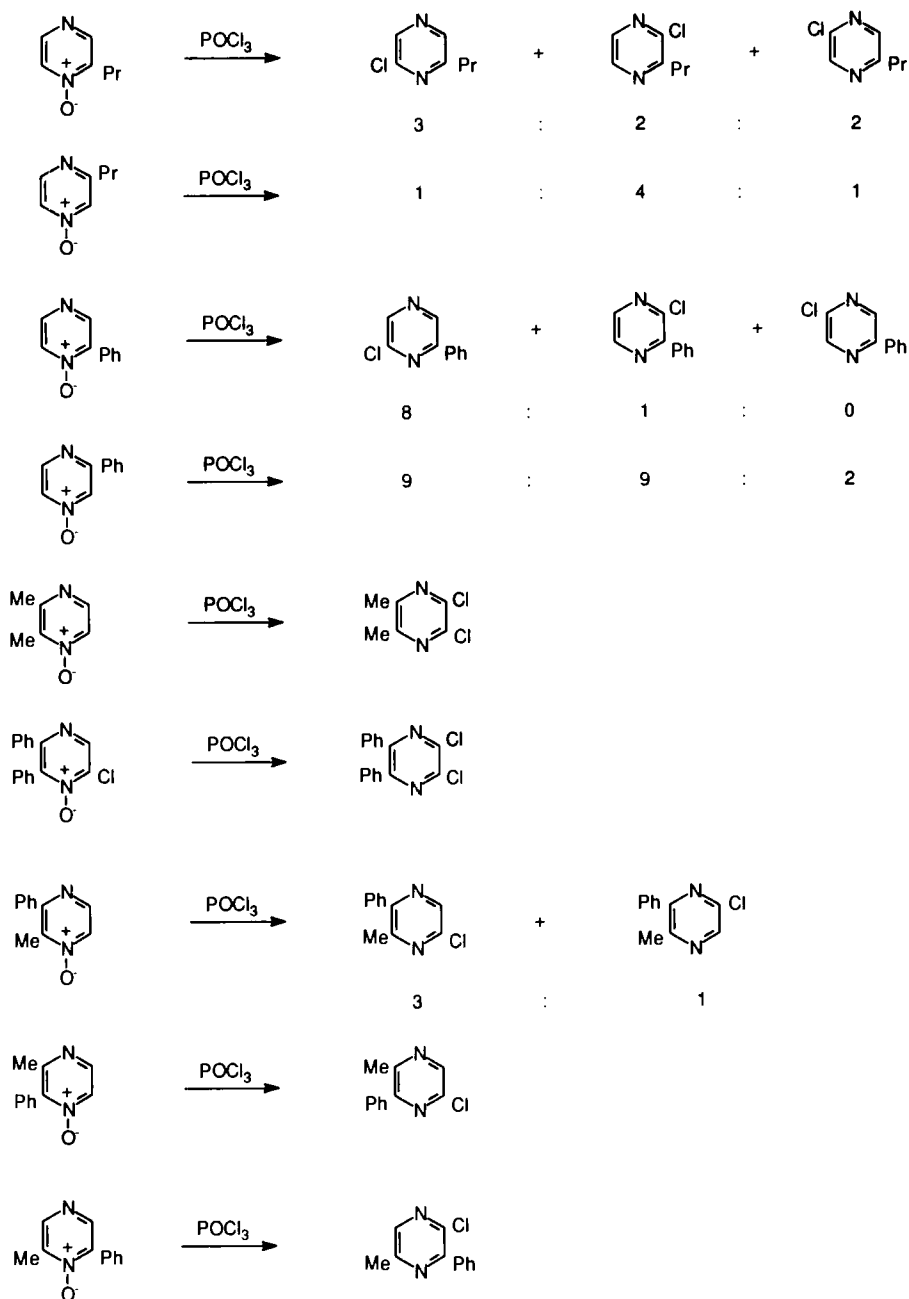
SCHEME 44

Elemental chlorine is able to chlorinate alkyl side chains; e.g., 2-methylpyrazine reacted with chlorine in acetic acid at 100°C to form mainly the trichloromethyl derivative (84M16).

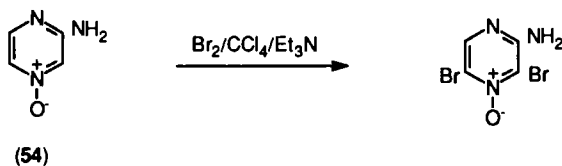
When pyrazine 1-oxides are treated with phosphoryl chloride the ring is deoxygenated and chlorine enters a position (usually) α - or β - to the oxide function. Pyrazine 1-oxide forms 2-chloropyrazine, and there are many other examples [69JAP69/12898, 69JAP69/20345; 82JHC465, 82JHC1061; 83H(20)991, 83JHC311; 84JCR(S)318; 85JHC1291; 86JHC149; 88AHC(44)199]. 3-Carbomethoxypyrazine 1-oxide, for example, formed a product in which chlorine had entered β to the original oxide group [69JAP69/20345]. An added complication of these Meisenheimer reactions is the propensity for alkylpyrazine *N*-oxides to give mixtures of annular and side-chain chlorinated products [83H(20)991; 85JHC1291; 86JHC149].

The studies of recent years have now clarified the observed orientations of nucleophilic chlorination. Calculations of π -densities for 2-methylpyrazine 1-oxide gave increasing electron densities of vacant ring positions in the order $6 < 5 < 3$. For the 2-phenyl compound the order was $6 < 3 < 5$; for 3-phenylpyrazine 1-oxide it was $2 < 6 < 5$. Experiment largely follows these predictions (82JHC1061). When there is more than one substituent already present in the *N*-oxide ring, annular chlorination is still possible, although some lateral chlorination may also be observed [85JHC1291; 86JHC149]. Heating with phosphoryl chloride transformed 3,5-dialkyl-, 3,5-diaryl-, and 3-alkyl-5-aryl-pyrazine 1-oxides into the 6-chloro derivatives (83JHC311). (Scheme 45) When there are different substituents in the 2- and 3-positions, mixtures of isomeric chlorides are usually formed, and in acetic anhydride both monochloro- and monoacetoxy-pyrazines result (82JHC465; 85JHC1291). Even in the presence of isopropyl and *sec*-butyl substituents most of the chlorination is annular; hydroxy groups are frequently replaced under these conditions (85JHC1291).

Heating with phosphoryl chloride converted 1-hydroxy-3-phenyl-2(1*H*)-pyrazinone (**52**) into the 2,5-dichloro derivative (**53**) via the 5-monochloro species. It had been expected that chlorination would take place at C-6, but this occurred only to a minor extent. The observed chloride attack β to the oxygen function might be accounted for in terms of the sequence illustrated in Scheme 46 (86JHC149). Reaction mechanisms have been proposed to explain the observed α - and β -chlorination when 2- and 3-substituted pyrazine *N*-oxides are subjected to the Meisenheimer reaction. β -Chlorination was rationalized in terms of electron withdrawal by the unoxidized nitrogen atom [84JCR(S)318] (Scheme 46).



SCHEME 45



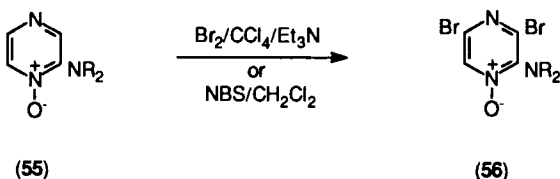
SCHEME 47

blocked the positions *ortho* and *para* to the hydroxy, however, no bromination would take place (56JA4071). Other examples of bromination of suitably activated pyrazines have appeared [83JAP(K)58/085872; 84MI19; 91H(32)2407].

The presence of an *N*-oxide function in pyrazine is not sufficient in itself to promote electrophilic halogenation, and even the presence of other weak donor groups may fail to promote reaction unless they can act in concert. Although 2-methoxypyrazine 1-oxide could not be brominated, the 3-methoxy isomer [and 3-aminopyrazine 1-oxide (54)] was brominated in the 2- and 6-positions (*ortho* to oxide and *ortho* or *para* to the amino group; cf. Scheme 47). Similarly, 2-aminopyrazine was brominated more readily than its *N*-oxide (55; R = H) where the two groups are in opposition [83JOC1064; 84H(22)1195].

The 6-position in the oxide becomes less activated than the 3- and 5-positions with the result that mixtures of 3-bromo (3–8%) and 3,5-dibromo (56; R = H) (20–30%) products are formed (cf. bromination of 2-aminopyrazine). A sterically demanding substituent such as 2-morpholino gave rise to the 5-bromo derivative exclusively (83JOC1064) (Scheme 48). Annular bromination of 2,3-dimethylpyrazine 1,4-dioxide could not be achieved (72CHE1153).

Conversion of pyrazinones into bromopyrazines is known (82MI2), as is side-chain bromination, particularly when NBS is used under conditions conducive to radical formation. Thus, 2-ethyl-3-methylpyrazine was converted into the 1'-bromoethyl derivative (72JOC511).

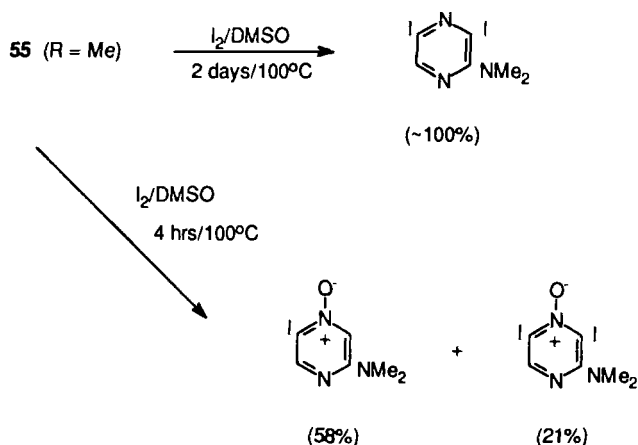


SCHEME 48

c. *Iodination.* Iodopyrazines are usually made by halogen exchange, from diazonium salts, or from the *N*-oxides (84M16). Iodine in dimethyl sulfoxide converted 2-dimethylaminopyrazine into more than 90% of a mixture of 5-iodo and 3,5-diiodo products [84H(22)1195], whereas NIS successfully iodinated some 2(1*H*)-pyrazinones in the 3- and 5-positions [91H(32)2407].

Iodination of **55** (R = Me) gave a mixture of 6-iodo and 2,6-diiodo derivatives along with some products of deoxygenation. Such deoxygenative halogenation is not as marked as in the pyrimidine *N*-oxides, and it usually requires extended heating with iodine in dimethyl sulfoxide [84H(22)1195] (Scheme 49).

d. *Fluorination.* Again, halogen-exchange processes have been the most useful. Tetrachloropyrazine reacted with anhydrous potassium fluoride at 310–320°C to form the tetrafluoro analogue, whereas milder conditions led to mixtures of chlorofluoro derivatives [70JCS(C)1023; 74M12]. Similar treatment of 2-chloropyrazine 1-oxide with potassium fluoride in dimethyl sulfoxide gave a 27% yield of the 2-fluoro 1-oxide. Heating the diazonium fluoroborate derived from 2-aminopyrazine 1-oxide with copper powder gave a 17% yield of the same product [84H(22)1105]. The Balz–Schiemann reaction has also been applied to the synthesis of 2-fluoropyrazine from the 2-amino heterocycle (66JHC435). Perfluoroalkylpyrazines were converted by cobalt(III) fluoride into products arising from loss of nitrogen, incidentally providing a novel route to some crowded perfluoroalkenes [81JCS(P1)2059].



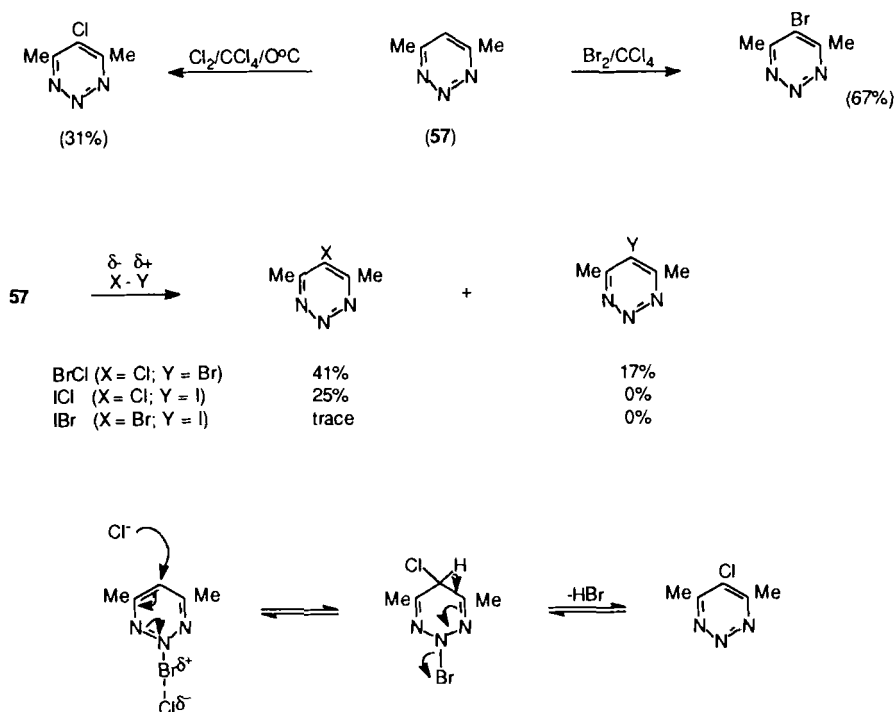
SCHEME 49

4. 1,2,3-Triazines

There have been no reports of electrophilic halogenation of 1,2,3-triazine [84MI7; 88AHC(44)199; 90AHC(47)325], but the 4,6-dimethyl derivative (**57**) was chlorinated and brominated (but not iodinated) under surprisingly mild conditions (86CPB4432) (Scheme 50). Repetition of these reactions using interhalogen reagents indicated that the more negative halogen was introduced preferentially. The process must then have been of the addition-elimination type.

When 1-aminopyrazoles were subjected to halogenation, preferential oxidation of the amino group led to 5-halogeno-1,2,3-triazines (88CPB3838) (see also Part I, Section B.1,a).

Nucleophilic displacement of chloro groups by fluoride was accomplished under pyrolysis conditions with potassium fluoride; the chloro (and bromo) precursors are available by ring-synthesis [78HC(33)1; 79CB1529; 84MI7]. Halogens next to annular nitrogens are the most easily displaced,



SCHEME 50

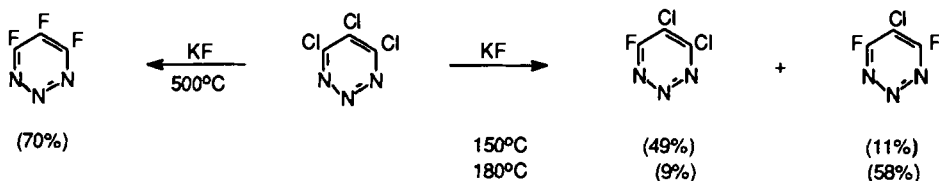
and yields of trifluoro-1,2,3-triazine approached 70% when the reaction was carried out under vacuum transfer conditions at around 500°C. Under less vigorous conditions mono- and di-fluorinated products eventuated (88T2583) (Scheme 51).

5. 1,2,4-Triazines

Again, direct halogenation of the parent has not been reported, and any electron-donating substituents present will not necessarily counteract the inherent resistance of the ring to electrophilic substitution [78HC(33)189; 84MI8; 88AHC(44)199; 90AHC(47)325]. Bromination of 3-amino-6-methyl-1,2,4-triazine was reported to give a 5-bromo derivative (64MI1; 71MI2), but Neunhoeffer believes that the original substrate was the 3-amino-5-methyl isomer that had been 6-brominated (84MI8). An oxy substituent in the 5-position was sufficiently activating to permit the 6-bromination of some 1,2,4-triazin-5-ones and -3,5-diones (61JOC1118). In aqueous sulfuric acid the 3,5-dione brominated 10^{10} times more slowly than uracil in reactions with mechanistic similarities (76JOC4004).

Although the presence of an *N*-oxide function was not sufficient to permit chlorination and bromination, both the 3-amino- and the 3-methoxy-1,2,4-triazine 1- (or 2-) oxides gave 6-halogeno derivatives. Halogenation would not take place with only chloro, methyl, or methylthio groups at C-3. All of the reactions were accompanied by a degree of deoxygenation, no doubt induced by the HBr or HCl formed in the reactions (77JOC3498; 78JOC2514; 83JOC1064).

Nucleophilic processes leading to halogenated derivatives include transformations of diazonium salts, especially for making fluorinated derivatives. 3-Fluoro-1,2,4-triazine 2-oxide was made in this way from the 3-amino derivative [85H(23)1969], and there are other examples (84MI8). Halogen exchange reactions, too, occur with some facility at all ring positions. A 6-bromo group has been replaced by chloride (90LA631), and all three chlorines of 3,5,6-trichloro-1,2,4-triazine were displaced when the



SCHEME 51

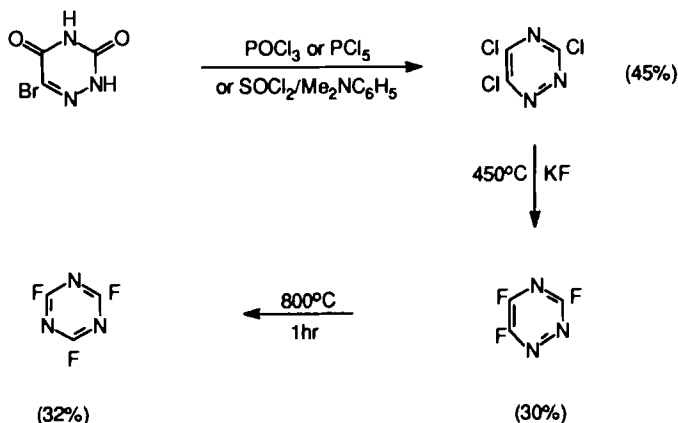
compound was heated at 450°C with potassium fluoride [80JCS(P1)2254; 82JCS(P1)1251] (Scheme 52).

There have been a number of examples in which an oxo group is replaced by chlorine using the customary reagents. Thus 3-oxo- (82CPB152), 5-oxo- [87H(26)3259; 90LA631], and 3,5-dioxo-compounds [82JCS(P1)1251] were transformed into the corresponding chloro derivatives, often in high yields (84–90%) [87H(26)3259]. Either phosphoryl or thionyl chlorides in the presence of dimethylaniline converted 3,6-disubstituted-2*H*-1,2,4-triazin-5-ones into the 5-chlorotriazines; phosphorus pentachloride gave the same product, but also induced some substituent chlorination. When the 6-position was vacant, thionyl chloride formed 3-substituted 5,6-dichloro-1,2,4-triazines (90LA631) (Scheme 31).

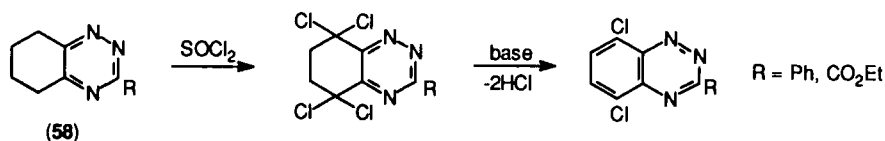
Alkyl groups attached to the triazine ring are quite prone to halogenation [77CCC2182; 84MI7; 89H(29)2253; 90H(31)1933]. A 70% yield of 6-dichloromethyl-5-trichloromethyl-2-phenyl-1,2,4-triazine was obtained when 5,6-dimethyl-2-phenyl-1,2,4-triazine was heated at 90°C with chlorine dissolved in an acetic acid–acetic anhydride–sodium acetate mixture [90H(31)1933]. Thionyl chloride similarly chlorinated **58** in the fused saturated ring [89H(29)2253] (Scheme 53).

6. 1,3,5-Triazines

Cyanuric chloride [2,4,6-trichloro-1,3,5-triazine; (**59**)] is the basis of three major industrial applications: triazine herbicides, triazine dyes, and optical whitening agents. It is not, however, made commercially by chlori-



SCHEME 52

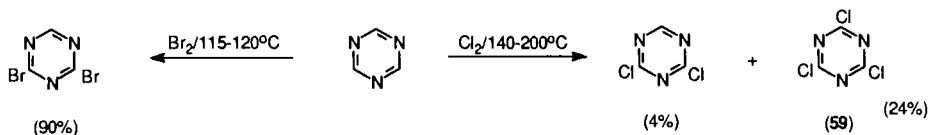


SCHEME 53

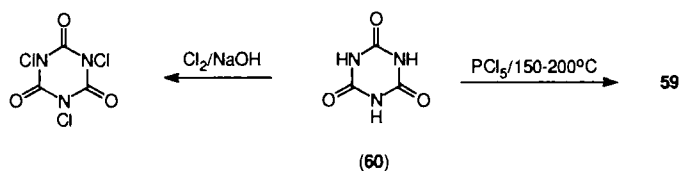
nation of 1,3,5-triazine, although such a process is feasible (74MI2; 84MI9). Chlorination and bromination of 1,3,5-triazine occur only under vigorous conditions with bromination being rather more successful. The reactions are probably not electrophilic [54JA632; 55JA44; 59HC(13)1; 63AG(E)309; 90AHC(47)325] (Scheme 54). Treatment of 1,3,5-triazine with chlorine or bromine at room temperature gave rise to "perhalides" (54JA632). Melamine (2,4,6-triamino-1,3,5-triazine) was halogenated to form products containing one to six halogens, depending on the reaction conditions [59HC(13)1]. Alkyl side chains on 1,3,5-triazine are quite readily α -halogenated by what are believed to be ionic mechanisms (64JOC1527).

Nucleophilic substitutions are complicated by the characteristic tendency of 1,3,5-triazines to undergo ring cleavage. Nevertheless, under forcing conditions, cyanuric acid (**60**) gave **59**. Chlorination in aqueous alkali, though, gave *N*-chloro derivatives [59HC(13)1; 79MI2] and bromine similarly *N*-brominated the tri-silver salt of **60** (67M1613) (Scheme 55).

Fluorinated 1,3,5-triazines are best made by the action of fluoride on the chloro analogues (63JOC1666; 73MI2). Sealed tube reaction of **59** with potassium fluoride resembled similar reactions of chlorinated pyrimidines [81JFC(17)385], and parallel reaction of 4-chloro-2,6-bis-isopropylamino-1,3,5-triazine in the presence of a catalytic amount of dicyclohexeno-18-crown-6 gave the 4-fluoro derivative in 93–99% yield [90CHE1142]. A 32% yield of 2,4,6-trifluoro-1,3,5-triazine resulted from extended pyrolysis of 3,5,6-trifluoro-1,2,4-triazine [80JCS(P1)2254; 82JCS(P1)1251] (Scheme 52). The trifluorotriazine is a useful fluorinating agent having been em-



SCHEME 54



SCHEME 55

ployed with advantage in conversions of hydroxyquinolines to the fluoro derivatives (60BRP845062).

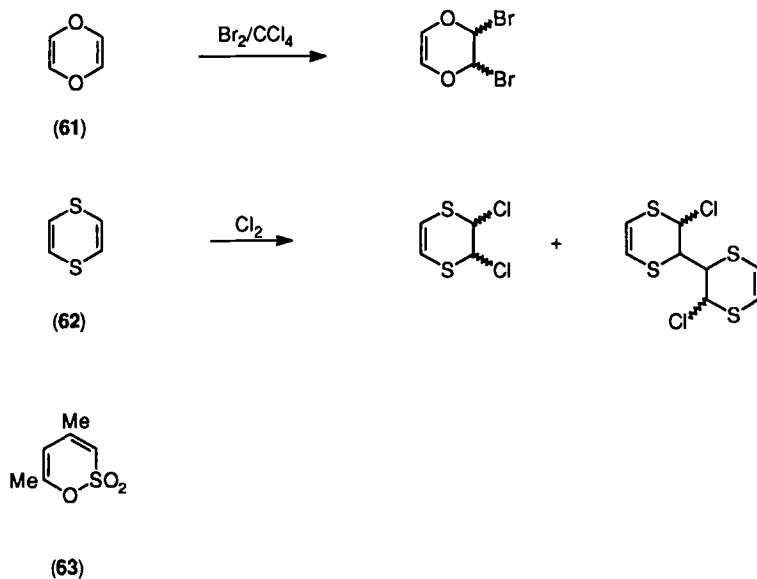
7. Tetrazines

Direct halogenation has not been reported for any of the possible tetrazine isomers, and halogenated derivatives are usually made by ring-synthesis or nucleophilic processes (84MI10). In the 1,2,4,5-tetrazines it was possible to replace a hydrazine function using chlorine or bromine in acetic acid (71CHE537; 78JHC445), perhaps via initial oxidation of the hydrazino group to diazonium.

C. SIX-MEMBERED RINGS WITH MORE THAN ONE OXYGEN OR SULFUR ATOM

The fully unsaturated compounds containing two oxygens (e.g., 1,4-dioxin; **61**), two sulfur atoms (e.g., 1,4-dithiin; **62**), and one each of oxygen and sulfur atoms (e.g., 1,4-oxathiin) are electron-rich and highly reactive toward electrophiles. Benzo derivatives are usually most reactive in the fused heteroring (84M113).

One molar equivalent of bromine in carbon tetrachloride gave the dibromo addition product with **61**; two molar equivalents or excess chlorine converted **61** into 2,3,5,6-tetrachloro-1,4-dioxane. The corresponding dithiin (**62**) reacted similarly with chlorine by addition (59JOC1819). Although 2,5-dimethyl-1,4-diithiin could not be halogenated, the 2,5-diphenyl derivative proved to be much more stable toward electrophiles, and could be mono- and di-brominated in the heterocyclic ring (61M11). In these reactions the compounds are reacting as cyclic alkenes, and they exhibit few if any aromatic properties (Scheme 56). Bromination of 4,6-dimethyl-1,2-oxathiin 2,2-dioxide (**63**) took place at the 3-position (69TL651).



SCHEME 56

D. SIX-MEMBERED RINGS WITH ONE NITROGEN AND EITHER OXYGEN OR SULFUR

Although 2-*H*-1,2-oxazines are unstable, the 1,3-isomers are quite well known. The 1,4-oxazines are relatively uncommon and unexplored. Aspects of the halogenation of oxazines and thiazines have been summarized (84MI14). Much more is known about the sulfur analogues, especially the benz derivatives of 1,4-thiazine (see Part 3). When perfluorinated 1-chloro-1,2-thiazine was heated with potassium fluoride, the chlorine was replaced by fluorine (92CB581).

A review article (86CHE1) that includes discussion of the properties of oxo- and thioxo-1,3-thiazines quoted C-5 as the most activated to electrophilic attack. Halogenation certainly occurs exclusively at this position even under very mild conditions. Molecular bromination of 4-hydroxy-2-phenyl-1,3-thiazin-6-one (**64**) proceeded satisfactorily in dioxan, carbon tetrachloride, or acetic acid with the highest yield of 5-bromo product being obtained in the last-named solvent, perhaps because **64** was more soluble in acetic acid. Iodination could only be accomplished using iodine monochloride [79CHE37; 90AHC(50)85].

The sultams (**65**) were brominated next to the annular sulfur atom (80MI1) (Scheme 57).



SCHEME 57

E. MISCELLANEOUS SIX-MEMBERED HETEROCYCLES WITH AT LEAST ONE ANNULAR NITROGEN

Little is known about the behavior of many of these compounds under halogenation conditions [84MI15; 90AHC(47)1]. Most reactions involve nucleophilic introduction of a halogen atom. Thus, the standard conversion of an oxo or hydroxy group into chloro is common. Heating with phosphorus pentachloride transformed 1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxides into the 4-chloro derivatives [80AG(E)131].

Electrophiles such as bromine and chlorine will, however, react with 1,2,6-thiadiazine 1,1-dioxides to give 4-halogeno derivatives [74JCS(P)2050], and the related thiadiazinone (**66**) also reacted in the 4-position with bromine in carbon tetrachloride to give a product that is a potent source of positive bromine [80JHC977].

Azaborines have received a little attention in recent years, particularly 1,2,3-diazaborines (**67**) [75ACS(B)1036; 76MI2; 84MI1] (Scheme 58). Bromine in pyridine converted 5-ethyl-1,2-dimethyl-1,2-dihydro-1,2,3-borazine into a mixture of 4- and 6-monobromo derivatives, and the 4,6-dibromo compound. With iodine monochloride the 4-iodo or 4,6-diiodo products formed, depending on the mole ratio of iodine monochloride to substrate [75ACS(B)461].



SCHEME 58



SCHEME 59

III. Heterocycles with Seven-Membered Rings

There are a number of ways in which halogen atoms can be introduced into diazepines and diazepinones [76H(4)1509; 78CR(C)(286)671; 84MI16, 84MI17]. Cations of type **68** have quasi-aromatic properties and can be halogenated in the 6-position under conditions that work successfully with benzene. Substituents in the 1-, 2-, and 4-positions may affect reactivity, and if C-6 is substituted by a phenyl group that group becomes *para*-brominated. The 2,3-dihydro-1,4-diazepinium salts are subject to ready electrophilic attack because the vinamidinium system is electron-rich, having six π -electrons spread over five atoms [74AHC(17)1; 78H(11)549; 89LA133].

Both NBS and NCS in methanol converted 1-methyl- and 1-phenyl-1*H*-azepin-3(2*H*)-ones into the 4-mono- or 4,5-di-halogenated products, depending on the molar ratio of reagent to substrate. Product yields varied between 41 and 60% (90JHC3163).

1,3,5,2,4-Trithiadiazepine (**69**), its benzo derivative, and 1,3,5,2,4,6-trithiatiazepine all were susceptible to electrophilic bromination [85CC396, 85CC398, 85CC1654; 86PAC197; 91JCS(P1)2945]. Treatment of the 6-acetyl derivative of **69** with NBS in acetonitrile gave a low yield (13%) of the 7-bromo product, whereas the 6,7-bis-mercured species is available through the thallium derivative [91JCS(P1)2945] (Scheme 59).

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56RTC1303
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58AG571
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59HC(13)1
59JOC11
59JOC1819
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